Evidence Report:

Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)

Human Research Program
Human Health Countermeasures Element

Approved for Public Release: April 07,2022

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

CURRENT CONTRIBUTING AUTHORS

Steven S. Laurie, PhD, KBR, Houston, TX.
Brandon R. Macias, PhD, NASA Johnson Space Center, Houston, TX.
Laura P. Pardon, OD, PhD, KBR, Houston, TX.
Tyson Brunstetter, OD, PhD, NASA Johnson Space Center, Houston, TX.
William J. Tarver, MD, MPH, NASA Johnson Space Center, Houston, TX.
C. Robert Gibson, OD, KBR, Houston, TX, USA, and Coastal Eye Associates Webster, TX.
Scott H. Greenwald, PhD, KBR, Houston, TX.
Karina Marshall-Goebel, PhD, KBR, Houston, TX.
Jessica V. Jasien, PhD, JES Tech, Houston, TX.
Sara Mason, BS, Aegis Aerospace, Houston, TX.
Ann Tsung, MD, MPH, KBR, Houston, TX.

ADDITIONAL AUTHORS CONTRIBUTING TO PREVIOUS VERSIONS

David J. Alexander, MD, NASA Johnson Space Center, Houston, TX.
Douglas R. Hamilton, MD, PhD, NASA Johnson Space Center, Houston, TX.
Stuart M. C. Lee, PhD, KBR, Houston, TX.
Thomas H. Mader, MD, Col (R), U.S. Army, Cooper Landing, AL.
Christian Otto, MD, Memorial Sloan Kettering Cancer Center New York, NY.
Cherie M. Oubre, PhD, NASA Johnson Space Center, Houston, TX.
Anastas F. Pass, OD, MS, JD, University of Houston, Houston, TX.
Steven H. Platts, PhD, NASA Johnson Space Center, Houston, TX.
Jessica M. Scott, PhD, Universities Space Research Association, Houston, TX.
Scott M. Smith, PhD, NASA Johnson Space Center, Houston, TX.
Michael B. Stenger, PhD, NASA Johnson Space Center, Houston, TX.
Christian M. Westby, PhD, Universities Space Research Association, Houston, TX.
Susana B. Zanello, PhD, Universities Space Research Association, Houston, TX.
Sara R. Zwart, PhD, University of Texas Medical Branch, Galveston, TX.

Table of Contents

ACRONYMS AND ABBREVIATIONS

AGBRESA	artificial gravity bed rest with the European Space Agency
AQP4	aquaporin-4
BM	Bruch's membrane
BMO	Bruch's membrane opening
cAG	continuous artificial gravity
CDM	carbon dioxide (CO_2) monitor
CSF	cerebrospinal fluid
CVP	central venous pressure
CWS	cotton wool spot
D	diopters
DAG	directed acyclic graph
FD	flight day
GF	globe flattening
Hcy	homocysteine
HDT	head-down tilt
HDTBR	head-down tilt bed rest
HRR	human research roadmap
iAG	intermittent artificial gravity
ICP	intracranial pressure
IIH	idiopathic intracranial hypertension
IIHTT	Idiopathic Intracranial Hypertension Treatment Trial
IJV	internal jugular vein
IOP	intraocular pressure
ISS	International Space Station
ITD	impedance threshold device
IVFA	intravenous fluorescein angiography
LBNP	lower body negative pressure
LC	lamina cribrosa
LDSF	long-duration spaceflight
MCI	multicolor imaging
miRNA	microRNA
MRI	magnetic resonance imaging
MRW	minimum rim width
MTHFR	methylenetetrahydrofolate reductase
MTRR	methionine synthase reductase
OCT	optical coherence tomography
ODE	optic disc edema
ONH	optic nerve head
ONSD	optic nerve sheath diameter
ONT	optic nerve tortuosity
PED	pigment epithelial detachment
RNFL	retinal nerve fiber layer
RPE	retinal pigment epithelium
SANS	spaceflight associated neuro-ocular syndrome
SD	standard deviation
SDSF	short-duration spaceflight

SEM	standard error of the mean
SHMT	serine hydroxymethyltransferase
SITA	Swedish Interactive Threshold Algorithm
SNP	single nucleotide polymorphism
STIR	short tau inversion recovery
TRT	total retinal thickness
USOS	US Orbital Segment
VESGEN	VESsel GENeration Analysis
VTC	veno-constrictive thigh cuffs

Trade names and trademarks are used in this report for identification only. Their usage does not constitute an official endorsement, either expressed or implied, by the National Aeronautics and Space Administration.

STATUS

Active: Work/research is currently being conducted to address this risk

EXECUTIVE SUMMARY

Ocular changes that include optic disc edema (ODE), globe flattening (GF), choroidal folds, and hyperopic shifts have been documented in astronauts during and after long-duration spaceflight (LDSF). NASA has termed this constellation of findings as spaceflight associated neuro-ocular syndrome (SANS). To date, about 70% of crewmembers who have participated in long-duration missions show one or more signs of SANS. The primary concern is that the changes in ocular structure may lead to uncorrectable vision changes either during or after a spaceflight mission. It is hypothesized that SANS findings are precipitated by the cephalad fluid shift crewmembers experience in chronic weightlessness during LDSF, but other genetic, anatomic, or spaceflight-related factors likely contribute to the interindividual variability of SANS findings. Although the underlying etiology linking the headward fluid shift to the development of SANS is not fully characterized, countermeasures that target reversal of the headward fluid shift currently represent the most promising approach to prevent or reverse the development of SANS. The headward fluid shift associated with exposure to weightlessness may affect several ocular fluid compartments, for example elevated cerebrospinal fluid (CSF) pressure may be transmitted down the optic nerve to the optic nerve head (ONH), localized accumulation of CSF and/or interstitial edema could occur at the ONH, or lymphatic or glymphatic fluid could be dysregulated at the ONH. Current and planned research is underway to characterize these possible factors.

Identifying an operationally feasible, effective countermeasure is a high priority for mitigating the SANS risk. Mechanical countermeasures that reverse the headward fluid shift are currently being investigated in a ground analog of spaceflight and in space. Ongoing efforts are determining if a nutritional supplement can prevent or limit the development of SANS findings.

Long-term follow up of crewmembers who have participated in LDSF missions will also provide valuable knowledge to establish any long-term health risks. The magnitude of ODE and/or choroidal folds, combined with the duration of exposure to these pathologies will likely determine the threshold for long-term risk. About 70% of crewmembers have the earliest signs of ODE, as determined by optical coherence tomography (OCT) imaging, but only about 15% of crewmembers develop clinically significant mild ODE, as evidenced by Frisén grade ≥ 1. Importantly, no documented cases of uncorrectable changes in visual acuity and no permanent changes to visual fields have been documented during or after LDSF. An ongoing effort is monitoring and investigating the long-term functional consequences of SANS after single or multiple LDSF missions.

New to this evidence report is the inclusion of brain structural changes that have been observed after LDSF. Multiple groups have established that spaceflight enlarges ventricles, but the clinical relevance of a ~1-3 ml (10-16%) increase in ventricle size still needs to be determined (Roberts et al. 2017; Alperin and Bagci 2018; Van Ombergen et al. 2018, 2019; Kramer et al. 2020; Hupfeld et al. 2020). Furthermore, an ongoing effort is determining if spaceflight-induced changes in brain and ocular structure represent independent responses to the chronic headward fluid shift due to weightlessness, or if they are directly related to each other.

As our understanding of the progression of SANS has evolved, the need to assess more specific ocular and brain functional outcomes, and to determine the long-term consequences of these outcomes is a high priority and is the subject of planned research. Commercial Crew missions will increase the number of crewmembers flying long-duration missions and provide expanded opportunities to study both veteran and novice flyers. Finally, the development of SANS findings during strict head-down tilt bed rest (HDTBR), as an analog of spaceflight-induced headward fluid shift, will allow countermeasures to be tested and possible individual contributing factors to be identified more rapidly. Both spaceflight and spaceflight analogs will be necessary to develop SANS monitoring capabilities and to assess the frequency, magnitude, and application of countermeasure(s) needed for crewmembers to safely complete future lunar and Mars missions.

SECTION I: EVIDENCE

Introduction

Ocular changes that include ODE, GF, choroidal folds, and hyperopic shifts have been documented in astronauts during and after LDSF. NASA has termed this constellation of findings as SANS. The primary concern is that these changes in ocular structure may lead to uncorrectable vision changes either during or after a spaceflight mission. Since the last update of this evidence report, teams of researchers, clinical investigators, and epidemiologists have narrowed the focus of SANS findings to the development of ODE, GF, chorioretinal folds, or substantial hyperopic shift in refractive error. Other changes to the structure of the eye that were discussed in previous reports of SANS findings, including cotton wool spots (CWS) and retinal hemorrhages, continue to be tracked but are no longer considered SANS findings.

Since the last publication of this evidence report, several peer-reviewed manuscripts have been published that enhance our understanding of SANS, including publications describing the first prospective observational longitudinal study of ocular findings (Macias et al. 2020); the first development of SANS findings in strict HDTBR, as an analog of the spaceflight-induced headward fluid shifts (Laurie et al. 2019, 2020b); the development of SANS findings in a second strict HDTBR that did not include elevated ambient PCO_2, demonstrating that elevated PCO_2 is not required to develop SANS findings (Laurie et al. 2021); early efforts to develop mechanical countermeasures that could be implemented during LDSF (Marshall-Goebel et al. 2021b); testing of an artificial gravity countermeasure during exposure to a spaceflight analog (Laurie et al. 2021); and changes in brain structure that included increases in ventricular volume after spaceflight (Roberts et al. 2017; Alperin and Bagci 2018; Van Ombergen et al. 2018, 2019; Kramer et al. 2020; Hupfeld et al. 2020). Because the optic nerve is an extension of the brain, ongoing work is focused on determining if and how the brain and eye changes are related and how this fits within the SANS risk framework.

Human Spaceflight Evidence

The clinical, research, and occupational surveillance groups collect each ocular finding and report the incidences based on the percentage of crewmembers flying long-duration missions (**Figure 1**). A more thorough discussion of each finding is described below.

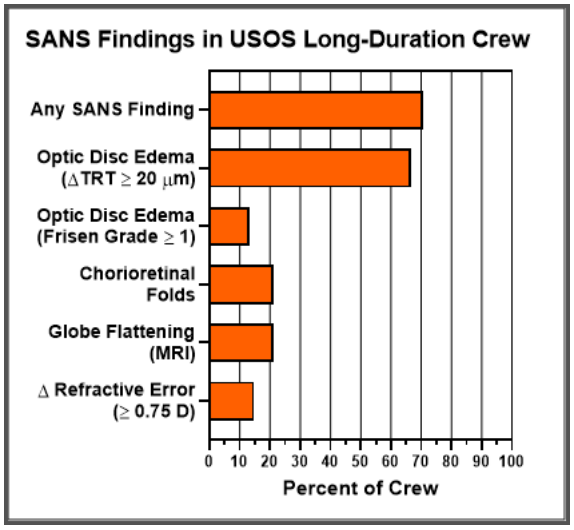

Figure 1. *Percent of crewmembers that present with ocular findings of SANS for all crewmembers in which data exist (courtesy of the NASA Lifetime Surveillance of Astronaut Health). SANS, spaceflight associated neuro-ocular syndrome; USOS, US Orbital Segment; ΔTRT, change in global total retinal thickness from Bruch's membrane opening to 250 μm; MRI, magnetic resonance imaging.*

Optic Disc Edema (ODE)

Fundoscopy

Direct clinical observation and photography have long been established as the terrestrial standard for documenting and monitoring the progression of ocular pathology including ODE. Introduced in 1982, the Frisén scale system is a standardized protocol to grade the appearance of the ONH in cases of edema, regardless of cause (e.g., elevated intracranial pressure (ICP), diabetes, anterior ischemic optic neuropathy, etc.) (Frisén 1982). The modified Frisén scale (Scott et al. 2010), which describes one key feature per grade, was originally used by NASA to grade the ODE observed in crewmembers; all Frisén grades throughout this report refer to the modified Frisén scale.

For decades, NASA's Flight Medicine Clinic team have performed fundoscopy-based evaluations and photography on the ground to document the preflight, postflight, and long-term retinal health of NASA's astronaut population. However, once SANS was established as a known spaceflight risk, in-flight fundus photography was introduced as an additional medical requirement. Beginning in 2009, a PanOptic™ ophthalmoscope (Welch Allyn, Inc., Skaneateles Falls, NY, USA) with a custom-mounted QuickCam web camera (Logitech, Lausanne, Switzerland) was used to collect fundoscopic images from astronauts on the International Space Station (ISS). In 2013, the Merge fundus camera (Merge Healthcare/OIS, Chicago, IL, USA) replaced the modified PanOptic™ device because of its superior resolution, operator interface, and overall usability. A new fundus camera, the Pictor Plus™ (Volk Optical, Mentor, OH, USA), was deployed to the ISS in 2021 to replace the Merge device.

Since 2019, most on-orbit retinal photographs have been obtained using the MultiColor Imaging (MCI) capability of the SPECTRALIS® OCT camera (Heidelberg Engineering, Heidelberg, Germany). MCI technology uses 3 scanning lasers of different wavelengths (i.e., green, blue, and infrared) to image ocular structures. When images obtained from these 3 lasers are combined, a "false color" photograph is generated that resembles the "true color" photographs obtained by traditional fundoscopy. Although MCI

is now the nominal technique used by NASA to obtain posterior pole photographs of deployed crewmembers, on-orbit fundoscopy sessions can be scheduled to obtain true color photographs when clinically indicated.

A 2008 Roscosmos Institute of Biomedical Problems publication (Mayasnikov and Stepanova 2008) discussed cerebral hemodynamics in cosmonauts participating in LDSF on the MIR space station. This publication provided a summary of various test results including postflight assessment of the ONH via ophthalmoscopy. The study involved 16 cosmonauts, and 8 cases of ODE were identified, ranging from "partial" to "moderate." Mild and moderate cases were diagnosed in at least 3 of the 16 crewmembers (i.e., a prevalence rate of approximately 19%).

Mader and colleagues (Mader et al. 2011) first described what is now known as SANS. Seven male astronauts were detailed in this report, all presenting with abnormal ophthalmic signs and symptoms thought to be a result of LDSF. Five of the 7 crewmembers were diagnosed with ODE: 2 with unilateral Frisén grade 1; one with bilateral Frisén grade 1; one with mildly-asymmetric bilateral Frisén grade 1; and one with asymmetric bilateral ODE (Frisén grade 3, right eye; Frisén grade 1, left eye). All of these ODE cases resolved after flight, usually within weeks of return to Earth (Mader et al. 2017). Mader and colleagues (Mader et al. 2013) reassessed one of these original 7 crewmembers after the crewmember completed a repeat LDSF about 9 years after his first LDSF. ODE had not been detected during or after his previous long-duration mission. However, unilateral Frisén grade 1 ODE in the right eye was diagnosed 5 months into his repeat LDSF and was confirmed after flight. Fundoscopy performed 52 days after flight documented resolution of the ODE.

Mader and colleagues (Mader et al. 2017) later described unilateral ODE in an additional crewmember who completed a 6-month mission in 2014. In this case, fundoscopy conducted during the flight documented mild ODE in the right eye by flight day (FD) 90. Although fundoscopy never detected ODE in the left eye during or after the flight, OCT scans detected signs of ODE by FD21 (right eye) and FD90 (left eye). This case was unusual in that the unilateral ODE (as diagnosed and monitored by fundoscopy) did not resolve until 20 months after landing.

Based solely on fundoscopy data, "clinically significant" ODE (i.e., Frisén grade ≥1) is diagnosed in about 15% of crewmembers during or after LDSF. About 90% of these cases are rated as Frisén grade 1, where edema extends 270-to-359 degrees around the optic disc circumference, presenting on fundoscopy as a C-shaped, blurred disc margin, with the edema originating on the nasal side of the ONH and progressing around the disc in clockwise and counterclockwise directions. More severe cases can present with a blurred disc margin that extends completely around the ONH (i.e., Frisén grade ≥2). Only one eye of one LDSF crewmember has been rated as Frisén grade 3, and none have been graded higher than 3. Many other LDSF crewmembers are diagnosed with "subclinical" ODE, a scenario where edema exists but does not meet the strict threshold of Frisén grade 1. Therefore, these cases are rated as Frisén grade 0.

The Frisén scale system is a valuable clinical tool; however, it has limitations. It relies on subjective interpretation, uses a noncontinuous categorical scale (e.g., grade 2 is not twice as severe as grade 1), is relatively insensitive (e.g., grade 0 does not necessary indicate an absence of edema), and has been shown to have wide interrater variability (Fischer et al. 2015). These concerns apply to terrestrial cases of ODE but are even more problematic for interpreting the mild or "subclinical" ODE cases typically observed in SANS. Therefore, a repeatable, objective test with higher sensitivity is preferred over fundoscopy for detecting and grading SANS-related ODE. Hence, quantitative and objective OCT approaches have been pursued to detect and monitor early signs of ODE (Patel et al. 2018; Laurie et al. 2020b).

Optical Coherence Tomography (OCT)

OCT provides high-resolution images of the ONH and the retina, allowing for objective quantification of these structures. Although 6-degree radius circular OCT scans centered on the ONH are often used in terrestrial clinical practice to quantify the thickness of the retinal nerve fiber layer (RNFL) and to assess optic nerve health, it has now been well-established that SANS related ODE is typically mild in nature and in most cases does not extend far enough into the retina to be detected at the sampling eccentricity of this conventional circle scan. Updated scan protocols implemented by NASA include concentric circle scans closer to the ONH, which should detect earlier changes; however, cross-sectional images through the ONH are more sensitive for identifying the earliest signs of ODE, which occur at the ONH (Hayreh 2016). Although spaceflight-induced ODE is generally thought to occur within the RNFL, as occurs in idiopathic intracranial hypertension (IIH), the RNFL becomes difficult to segment near the ONH. For this reason, and because previous studies have found total retinal thickness (TRT) outperforms RNFL for detecting disc edema (Scott et al. 2010; Vartin C et al. 2012), TRT is the primary metric used to identify SANS related ODE.

TRT in an annular region extending from Bruch's membrane opening (BMO) to a 250 µm retinal eccentricity (**Figure 2**) provides a region of interest surrounding the ONH that can be objectively and repeatedly measured, as first described by Patel, *et al.* (Patel et al. 2018). A repeatability analysis was conducted on data derived from OCT images collected in 7 astronauts who had never flown in space; these astronauts were studied during multiple body postures on different days separated by 4 months, and OCT scans were analyzed by different readers. This analysis was used to estimate the 95% confidence interval for variability in TRT from BMO-250 µm that results from normal physiological changes and from measurement variability, and a change in TRT (i.e., ΔTRT) exceeding 19.4 µm was determined as the earliest signs of ODE (Laurie et al. 2020b). Because of concerns that ODE may continue to progress during longer duration spaceflight missions, this threshold is now used to determine if an astronaut has developed the earliest signs of ODE and requires increased monitoring. Although only about 15% of crewmembers develop Frisén grade edema ≥1 during LDSF, approximately 70% of astronauts have early signs of ODE as detected by OCT quantification of TRT adjacent to the ONH.

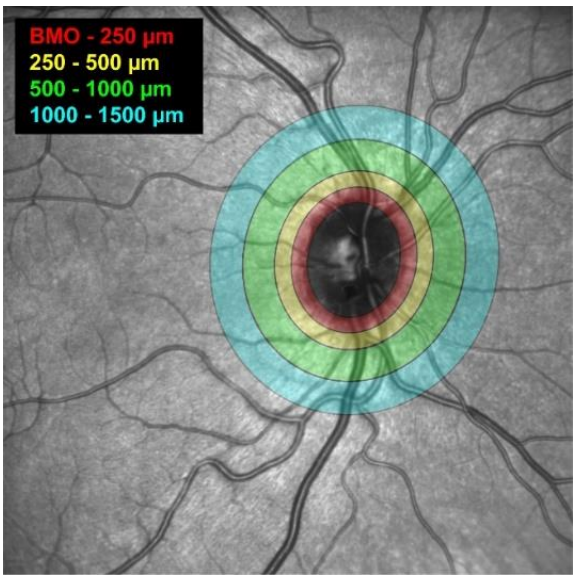

Figure 2. *Regions of interest are quantified based on segmentations from radial optical coherence tomography images centered over the optic nerve head (not shown). Annular regions over which TRT is quantified include: (1) BMO to 250 µm (red); (2) 250 to 500 µm (yellow); (3) 500 to 1000 µm (green); and (4) 1000 to 1500 µm (cyan). The innermost region, extending from the BMO to 250 µm, is used to identify the presence of ODE; ΔTRT that exceeds 19.4 µm, the normal measurement variability at this location (Laurie et al. 2020b), is considered to be disc edema. TRT, total retinal thickness; BMO, Bruch's membrane opening; ODE, optic disc edema.*

Optic disc cube scans obtained using Cirrus HD-OCT (Carl Zeiss Meditec) that were collected before 2013 were used to measure TRT and RNFL thickness in 15 astronauts before and after their spaceflights of about 6-months on the ISS; thickness measures were assessed within the ONH (i.e., region within a best-fit ellipse to BMO) and in 4 annular regions adjacent to the ONH: (1) BMO to 250 µm; (2) 250 to 500 µm; (3) 500 to 1000 µm; and (4) 1000 to 1500 µm (Patel et al. 2018). Relative to before flight, TRT was significantly increased after flight from within the ONH to an eccentricity of 1000 µm, whereas the thickness of the RNFL only increased to an eccentricity of 500 µm. For both measures, superior, inferior, and nasal quadrants were affected, and changes in thickness were greatest in regions close to the ONH.

In 2013, a SPECTRALIS OCT (Heidelberg Engineering) was sent to the ISS, allowing crewmembers to capture OCT images during flight for the first time. A similar SPECTRALIS OCT was used to collect scans on the ground before and after flight, which allowed scans to be linked in follow-up mode, ensuring consistent anatomical alignment. The first prospective SANS observational study of astronauts after the initial report of ODE in 2011, the Ocular Health Study, made use of these new OCT capabilities and has provided the most information regarding the development and resolution of ODE during and after spaceflight. The Ocular Health Study assessed changes in ocular structure during 6-month-long spaceflight missions, and determined whether these changes persist up to one year after return to Earth (Macias et al. 2020). TRT was quantified from radial OCT scans of both eyes of 11 astronauts using the same annular regions as Patel et al. (Patel et al. 2018), and minimum rim width (MRW), a sensitive measure that has been used to detect subtle thinning and thickening of the neuroretinal rim (Chauhan et al. 2013; Patel et al. 2014; Pardon et al. 2020), was assessed to quantify tissue within the ONH. MRW increased an average of 12.5 µm on FD10 and 35.7 µm on FD150. Similarly, TRT from BMO to 250 µm increased by 11.9 µm and 27.6 µm on FD10 and FD150, respectively. TRT from 250 to 500 µm also increased at these time points, although the magnitude of change was less (4.7 µm and 12.9 µm on FD10 and FD150, respectively). MRW and TRT followed similar recovery profiles, returning to approximately baseline values 90 days after return to Earth.

Contrary to previous anecdotal reports suggesting that SANS occurs more frequently in males and primarily affects right eyes, the data from the Ocular Health Study demonstrated that ODE develops in both sexes with no apparent preference for eye laterality during spaceflight. After return to the gravitational environment on Earth, and without any additional treatment, ODE as quantified by TRT recovered over weeks to months in most astronauts, although TRT in some astronauts had still not returned to preflight levels 1 year after return. Additionally, crewmembers who flew on missions lasting up to 1 year continued to have thickened TRT values throughout the mission and demonstrated a partial rapid recovery in the first few days after return to Earth followed by a continued slow recovery thereafter (Macias et al. 2021) (**Figure 3**). A change in TRT > 19.4 µm was detected in 15 of the 21 eyes analyzed (71%), suggesting the earliest signs of ODE; this is similar to the data from the NASA Lifetime Surveillance of Astronaut Health in **Figure 1** showing that 67% of all crewmembers with OCT had an increase in TRT that exceeded this threshold.

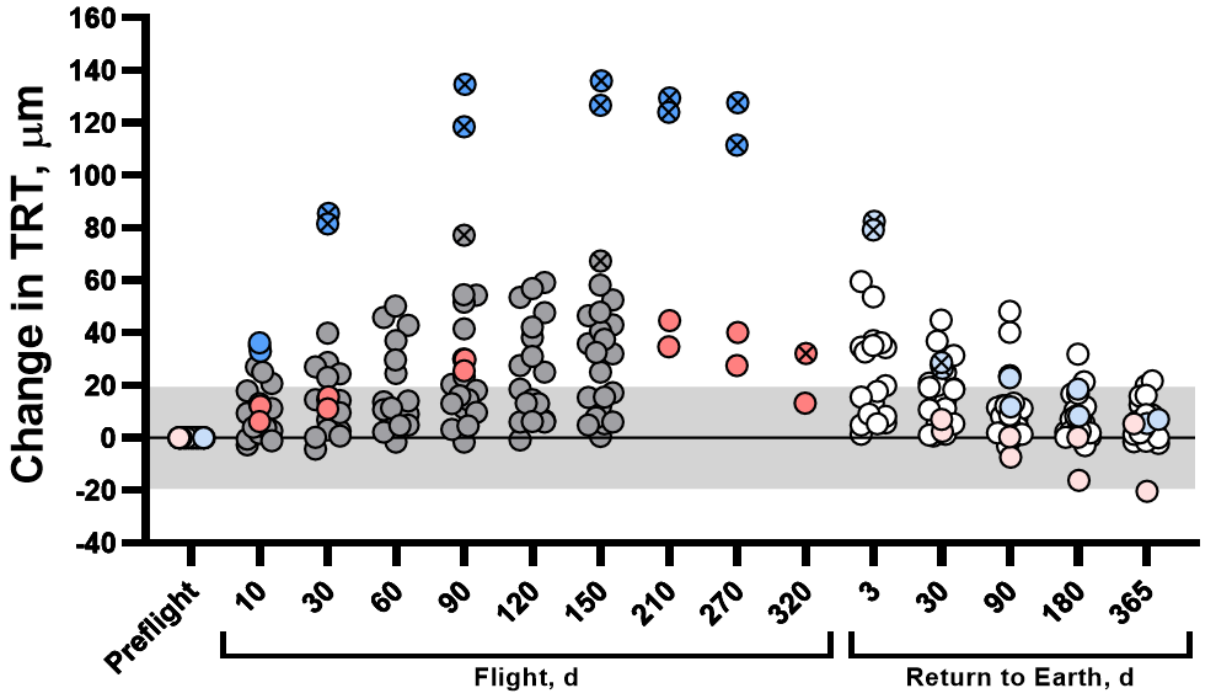

Figure 3. Change in TRT from Bruch's membrane opening to 250 µm relative to preflight values both during and after long-duration spaceflight. Circles represent individual data from each eye, and circles with an X inside represent eyes with optic disc edema based on fundoscopy. Grey in-flight symbols represent crewmembers who flew ~6-month missions. Red and blue symbols represent crewmembers who flew ~1-year missions. Light grey region spanning from ±19.4 µm represents the threshold for determining the earliest signs of optic disc edema. TRT, total retinal thickness. (Modified from Macias et al., JAMA Ophthalmology, 2021).

Chorioretinal Folds

Chorioretinal folds have been documented using fundoscopy or OCT in about 20% of NASA and partner Space Agency crewmembers who have participated in LDSF missions (**Figure 1**). Thus far, all chorioretinal folds reported in this population were classified as either choroidal folds or retinal folds (Mader et al. 2017), as defined by the Idiopathic Hypertension Treatment Trial (Sibony et al. 2015). Choroidal folds are undulations of Bruch's membrane (BM) and the retinal pigment epithelium (RPE), which are non-neural laminar structures located adjacent to the anterior side of choroid (**Figure 4**). Retinal folds are undulations of the inner retinal surface or intra-retinal tissue that are not in the immediate proximity of the optic disc (i.e., not peripapillary) (Sibony et al. 2015) (**Figure 4**). The progression of chorioretinal fold development is hypothesized to correlate with the duration of exposure to chronic weightlessness, as supported by the observation that submacular choroidal folds progressively worsened during a crewmember's 1-year mission on the ISS (Macias et al. 2021). Chorioretinal folds can resolve gradually during the months after a mission; however, they have persisted for years in some individuals (Mader et al. 2011, 2017) and could be permanent in those cases. If fold development advances with mission duration, it is possible that the fovea will be affected during exploration class missions, potentially resulting in debilitating, uncorrectable central vision defects. Choroidal folds have been observed at the

fovea in a small number of crewmembers during spaceflight, but were not associated with any changes in vision.

In terrestrial populations, chorioretinal folds can be caused by low intraocular pressure (IOP) and low scleral rigidity (Fannin et al. 2003; Thomas et al. 2015; Osigian et al. 2018), and by pathologically elevated ICP (Sibony et al. 2015). However, these mechanisms do not appear to explain chorioretinal fold development in astronauts. Ocular hypotony is not observed during spaceflight (Draeger et al. 1995; Greenwald et al. 2021), and evidence from short periods of weightlessness during parabolic flight indicate that weightlessness does not result in pathologically high ICP (Lawley et al. 2017); ICP has not yet been measured in astronauts during LDSF. Alternatively, the anterior expansion of the choroid and GF that occur during spaceflight (Friberg 1989; Mader et al. 2011; Macias et al. 2020; Greenwald et al. 2021) have been hypothesized to produce folds by compressing the choriocapillaris and retina (Friberg 1989), but these mechanisms have not been confirmed. The etiology of chorioretinal folds that develop during spaceflight remains an open question.

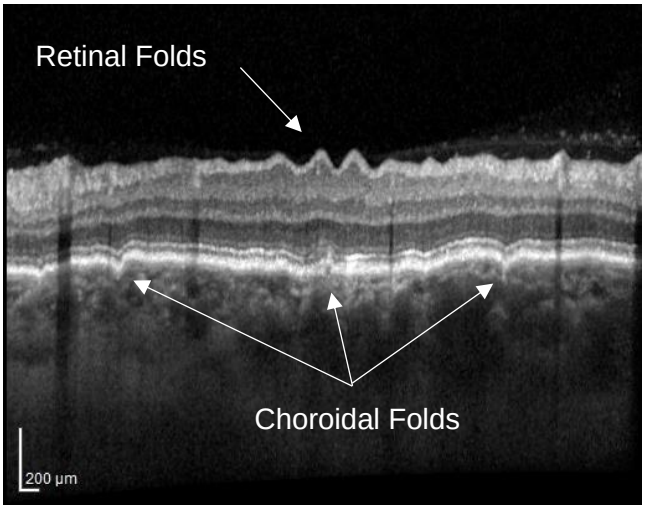

***Figure 4**. Chorioretinal folds can develop during spaceflight.* A cross-sectional optical coherence tomography image with choroidal folds and retinal folds in a crewmember who participated in a long-duration mission. Image courtesy NASA, Lifetime Surveillance of Astronaut Health

Globe Flattening (GF)

GF in astronauts can be determined at the ONH and at the macula. The subjective reports of GF described in the seminal report (Mader et al. 2011)and in a follow up study (Mader et al. 2021) reflected globe morphology at the ONH during the clinical read of the ocular magnetic resonance imaging (MRI). Although this approach has provided insight into the prevalence of GF after LDSF, quantitative assessment of GF may provide greater sensitivity and reliability for determining the development and progression, or regression, of SANS signs. In addition, preflight and postflight measurements of axial length measured using an optical biometer (IOL Master 700, Zeiss) reveal relatively small amounts of GF at the macula (Macias et al. 2020). It is important that any discussion of GF and its possible influence on changes in refractive error clearly states whether the measure is being obtained at ONH or at the macula (i.e., axial length).

Subjective measures determined an incidence of GF in one astronaut that began during flight (based on ultrasound imaging) and was detected after LDSF (Mader et al. 2017). The use of MRI for this case study was subjective, as the quantitative changes to the ocular globe and distention of the optic nerve

sheath diameter (ONSD) were not calculated. Optical biometry revealed a reduction in axial length of 0.53 mm (right eye) and 0.29 mm (left eye), consistent with GF that persisted for at least 5 years after flight. Ocular MRI suggested persistent GF at the ONH 7 years after flight. However, GF and ONSD distention were observed in 3 astronauts up to 3 years before spaceflight travel (Mader et al. 2021), highlighting the importance of assessing the change in GF relative to the preflight measure. Together, these data suggest that the posterior sclera may be permanently altered after LDSF and highlight the need for improved objective metrics for tracking the development of GF during and after spaceflight.

A means to quantitatively assess changes in posterior globe morphology has been developed for patients with IIH by creating a 2-dimensional (2D) map of the distances from the globe center to the posterior scleral wall (Alperin et al. 2013). This approach was first used to quantify GF metrics in 7 IIH patients with bilateral papilledema (mean Frisén grade of 2.0) (Alperin et al. 2013) and later demonstrated a greater change in ONH GF in 7 crewmembers of LDSF missions than the change in 9 crewmembers of short-duration spaceflight (SDSF) missions (Alperin and Bagci 2018).

More recently, MRIs collected from 10 astronauts before and after LDSF were analyzed to quantify GF at the ONH (Sater et al. 2021). This prospective study obtained measures in crewmembers after LDSF, regardless of SANS status. Most astronauts had GF at the ONH, with a mean ± standard error of the mean (SEM) postflight displacement of 9.88 ± 5.31 mm^3 ($p < 0.001$) at R+1 and 7.21 ± 5.39 mm^3 ($p < 0.01$) at R+360 quantified from the 4 mm diameter region of interest surrounding the ONH. This displacement resulted in the ONH moving anteriorly by a mean ± SEM of 200 ± 110 µm on R+1 and 140 ± 100 µm at R+360; however, these values are considered small relative to the total volume of the globe. Conversely, the axial length measures to the fovea demonstrated a smaller degree of shortening with a mean ± SEM of 120 ± 70 µm at R+1 and 60 ± 70 µm at R+360, highlighting the need to independently assess changes at each the ONH and macula. The crewmember with the greatest displacement of vitreous chamber volume (right eye: 39.16 mm^3; left eye 22.43 mm^3) also developed Frisén grade ODE (Sater et al. 2021). These data highlight that objectively quantifying GF at the ONH can determine the magnitude of this affect in crewmembers after spaceflight and in test subjects participating in spaceflight analog studies. Work is underway to determine the precision of this measure and to determine the magnitude for a physiologically meaningful change.

Refractive Error

Refractive error is a measurement of the lens power needed to correctly focus light on the retina of the eye. Myopia (near-sightedness) occurs when light focuses in front of the retina and is corrected with minus lenses, and hyperopia (far-sightedness) is when light focuses behind the retina and is corrected with plus lenses. Myopic patients experience blurred distance vision, whereas hyperopic patients may experience eyestrain and/or blurred near vision if their accommodative system (i.e., system that focuses the eye by changing the shape of the crystalline lens) is not able to compensate for their hyperopic refractive error. There is a loss of accommodative reserve with aging, making it more difficult for an individual to overcome hyperopic refractive error with increasing age, particularly over the age of 40.

Two types of refraction tests, manifest and cycloplegic, are used to measure refractive error. In manifest refraction, refractive errors are measured while the eye's own crystalline lens remains able to accommodate. During manifest refraction, subjects may "over-use" their accommodative ability while trying to read a line of letters. This must be controlled to accurately determine the refractive error and prescribe the appropriate correction. Cycloplegic refraction determines refractive error while the muscles that aid in focusing the eye are temporarily paralyzed. Cycloplegic eye drops (e.g., tropicamide 1%

ophthalmic solution) are used to temporarily relax the ciliary muscle, the "focusing" muscle that affects the shape of the lens. The changes in refractive error described in this section are based on cycloplegic refraction. This cycloplegic testing is only performed before and after spaceflight because a reliable and sensitive method of measuring refractive error is not currently available on the ISS.

Medical tests, research, and anecdotal reports have identified spaceflight-associated alterations in visual acuity over the last 40 years. In 2011, the seminal report by Mader and colleagues (Mader et al. 2011) provided case studies of 7 ISS astronauts who participated in LDSFs and underwent extensive postflight medical examinations after they reported changes in their near visual acuity. The hyperopic shifts were almost entirely spherical in nature, with little if any cylindrical component. Five of the 7 astronauts who reported altered near vision had a pre- to post-mission hyperopic shift that was equal to or greater than +0.50 diopters (D) spherical equivalent refractive error in one or both eyes (range +0.50 D to +1.50 D), and most of these astronauts reported diminished visual acuity that persisted after the mission. It is important to note, however, that all astronauts with changes in refractive error to date have had vision that was correctable to 20/20 or better with an updated spectacle and/or contact lens prescription.

Changes in visual acuity are not uncommon in astronauts, and there appears to be a higher prevalence among crewmembers who participate in LDSF. Specifically, 29% of crewmembers who participated in a short-duration Shuttle spaceflight and 60% of crewmembers who participated in LDSF have reported degradation of distance or near visual acuity (Mader et al. 2011). Astronauts completing LDSF have also demonstrated greater shifts in refractive error than experienced by astronauts completing SDSF, with shifts up to +2.00 D during a single mission documented after return from LDSF. Although refractive error returned to preflight baseline levels for all SDSF astronauts, refractive error remained altered years later for some LDSF crewmembers. However, an "excessive refractive error shift" (i.e., ≥ +0.75 D [spherical/cycloplegic] during a 6-month mission) has only occurred in about 15% of crewmembers tested after LDSF; this limit was selected because a change of this magnitude would be unlikely to occur over the same period of time on Earth in the absence of a pathological condition.

Multiple factors have been proposed as potentially contributing to a hyperopic shift, including GF, choroidal thickening, and changes to the optical components of the eye. GF could reduce the axial length of the eye, resulting in a hyperopic shift in vision. However, as noted in the GF section of this report, GF measured at the ONH, where the majority of data have been reported, is not necessarily accompanied by axial shortening at the macula. To influence refractive error, GF at the ONH would need to be severe enough to extend to the foveal region. Axial length at the fovea is commonly measured with optical biometry, and this has been quantified in astronauts. As part of the Ocular Health Study, optical biometry (IOLMaster 500, Zeiss) was performed before flight and within 7 days of return to Earth (Macias et al. 2020), providing measures of both axial length and anterior chamber depth. On average, axial length decreased by 0.08 mm. This change would be expected to result in a small hyperopic shift, as a 1 D change in refractive error has been reported to correspond with an axial length change of ~0.35 mm (Atchison et al. 2004). Anterior chamber depth also decreased after flight by an average of 0.09 mm; this would counteract the effects of a decrease in axial length because a decrease in anterior chamber depth would be expected to result in a myopic shift in refractive error due to the decreased distance between the cornea and crystalline lens (i.e, the combined optical power of the cornea and lens is greater when the 2 optical components are closer together, causing light to converge more anteriorly). Spherical equivalent refractive error shifted by +0.13 D after flight for this cohort, and this change persisted for at least 6

months after return to Earth. These data reflect measures obtained after spaceflight, and it is possible that greater changes occur during flight that partially resolve by the time optical biometry data are collected on Earth. Since 2020, measures of axial length on all crewmembers have been collected using a newly released version of this device (IOLMaster 700, Zeiss).

As with GF, an increase in choroid thickness could reduce the distance from the front of the cornea to the retina, thereby resulting in a hyperopic shift in refractive error. As part of the Fluid Shifts Study, choroid thickness was measured over a 3 mm region centered under the fovea and was found to increase an average of 35 µm during spaceflight (Greenwald et al. 2021). This amount of anterior movement of the retina would likely have a minimal effect on refractive error. Changes in axial length due to choroidal thickening would, in theory, be captured by optical biometry, which measures axial length as the distance between the anterior corneal surface and the RPE; however, choroid thickness measured within 3 days of return to Earth had already partially recovered compared to the last inflight measure (Macias et al. 2020), suggesting that optical biometry measures obtained within the first week after flight may underestimate any contribution of choroid thickness to changes in axial length during spaceflight. In addition to GF and choroidal thickening, which are thought to move the retina anteriorly, refractive error may be influenced by changes to the optical components of the eye, including potential changes in corneal curvature, corneal thickness, crystalline lens position, and lens thickness.

Other Ocular Findings

In addition to the ocular findings discussed above that are included in the definition of SANS, additional ocular findings have been observed in crewmembers during and after LDSF and are tracked by NASA.

Increased Choroidal Thickness

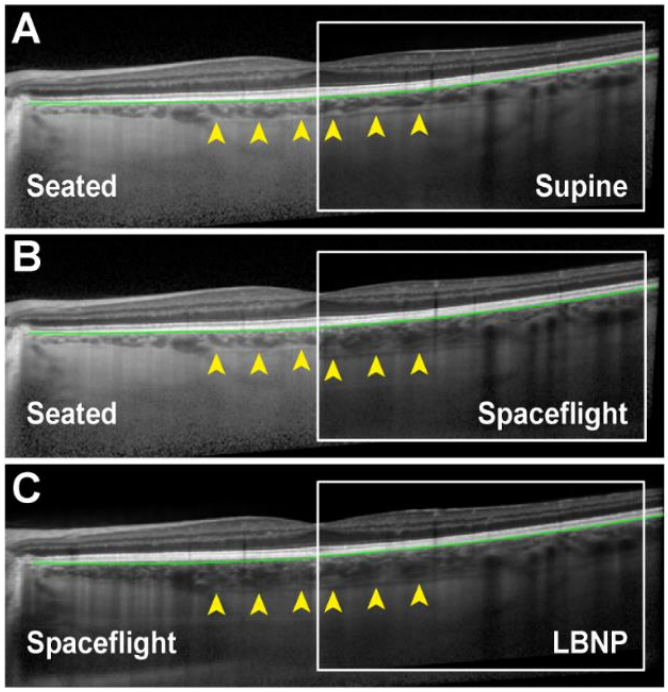

Figure 5. Choroidal expansion during spaceflight. The optical coherence tomography (OCT) images shown are from a single subject; Bruch's membrane is segmented (green line) and the chorioscleral border is marked (yellow arrowheads). ***A)*** *An acute seated (left) to supine (inset, right) posture change does not affect choroidal thickness.* ***B)*** *In comparison to the measurements acquired in the seated posture (left), the choroid expands during spaceflight (inset, right).* ***C)*** *Choroidal thickness during spaceflight (left) is not affected by exposure to 25 mmHg of LBNP (inset, right). LBNP, lower body negative pressure. Adapted from Greenwald,* et al. J. Applied Physiology, *2021.*

The choroid thickens during spaceflight (**Figure 5**), presumably as a consequence of the headward fluid shift (Mader et al. 2017; Laurie et al. 2020b; Macias et al. 2020; Greenwald et al. 2021). However, neither the specific mechanisms by which this structural alteration occurs nor how ocular health may be affected are fully understood. The average increase in choroidal thickness across crewmembers (n=13 subjects) at ~1 month in weightlessness is ~30 µm (Laurie et al. 2020b), which exceeds the modeled variability for this measurement (Marshall-Goebel et al. 2021b), and 2 long-duration mission studies (n=13 subjects; n=11 subjects) have reported that the mean increase reaches ~40 µm during the initial 5 months in weightlessness (Macias et al. 2020; Greenwald et al. 2021). However, the change can be substantially greater for individual crewmembers, as increases of up to 174 µm have been documented during a 6-month spaceflight mission (Greenwald et al. 2021). Following return to Earth after a 6-month mission, choroidal thickness gradually returns to preflight values, typically taking 3 to 6 months to fully recover (Macias et al. 2020). There appears to be an initial rapid decrease in thickness, as evidenced by the difference from the last inflight measure to the first postflight measure 1-3 days after return to Earth, followed by a slower recovery over months (Macias et al. 2020).

Choroidal engorgement is hypothesized to be caused primarily by cerebral venous congestion that impedes outflow via the vortex veins. However, choroidal thickness values are unaffected by a 15-minute exposure to LBNP (25 mmHg) during spaceflight, suggesting the involvement of a mechanism(s) that occurs as a secondary effect of the cerebral venous congestion; chronic choroidal vessel distension and enhanced capillary filtration are possible candidates (Greenwald et al. 2021). Interestingly, use of the spaceflight analog strict HDTBR, which induces thickening of the peripapillary retina and development of ODE (likely due to the chronic headward fluid shift), does not result in choroidal expansion as occurs during spaceflight (Laurie et al. 2020b, 2021). The cause for this difference is intriguing, but not understood. One consideration is that, in contrast to spaceflight conditions, gravity in the vertical axis (Gz) during bed rest generates tissue weight, perhaps impeding choroidal expansion. Another consideration is that venous flow patterns documented during spaceflight (Marshall-Goebel et al. 2019) have not been observed during bed rest. The anterior expansion of the choroid during spaceflight has been speculated

to contribute to SANS-related hyperopic shifts, but as discussed above in the *Refractive Error* section, it is unlikely that this mechanism fully explains the effect. Understanding whether and how astronauts' eyes are affected by choroidal engorgement will require further investigation.

Cotton Wool Spots (CWS)

CWS were first described in the sentinel report by Mader and colleagues (Mader et al. 2011), but whether these findings were truly associated with SANS or were due to other factor(s) is not yet clear. In a terrestrial environment, CWS are extremely rare in healthy adults but are well-documented in chronic diseases such as advanced hypertension, Purtscher retinopathy, high altitude exposure, diabetes, AIDS, and other severe disease states. A retrospective review of astronaut CWS cases revealed that most of these findings occurred during postflight testing, typically a month or even years after flight. Terrestrial radiation therapy is also known to produce CWS weeks to years after the radiation exposure, and astronaut exposure to a comparatively low but prolonged dose of space radiation has been proposed as a possible cause of CWS during or after spaceflight (Mader et al. 2017); however, research is needed to determine if the radiation doses experienced by crewmembers on ISS, levels much less than those incurred during radiation therapy, would be sufficient to cause CWS. A total of 8 individuals have presented with a CWS, and the time point of each diagnosis is shown below (**Figure 6**).

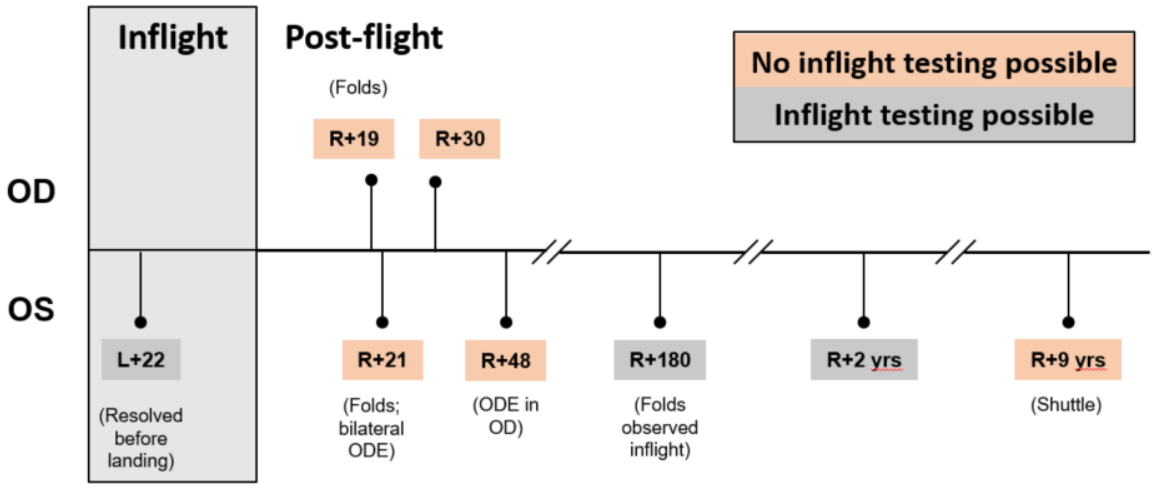

***Figure 6**. Six cases of cotton wool spots have been observed in the left eye (OS), and 2 have been observed in the right eye (OD). Additional details about the individuals presenting with each case are provided, including whether they had other SANS findings and if testing was or was not available during spaceflight. L, launch. R, return. ODE, optic disc edema.*

Retinal Cysts and Pigment Epithelial Detachments (PEDs)

Non-impactful retinal defects have also been detected in multiple crewmembers during nominal on-orbit OCT data collections. Many of these discoveries have occurred after 2019, when higher density scan patterns were incorporated into the US Orbital Segment (USOS) OCT protocol. These defects include intraretinal cysts and retinal PEDs. On-orbit intraretinal cysts tend to develop adjacent to the ONH (red arrow, **Figure 7**). Cysts have also been detected within the ONH (yellow arrow, **Figure 7**). To date, they tend to be isolated, do not affect the crewmember's vision, and resolve after return to Earth.

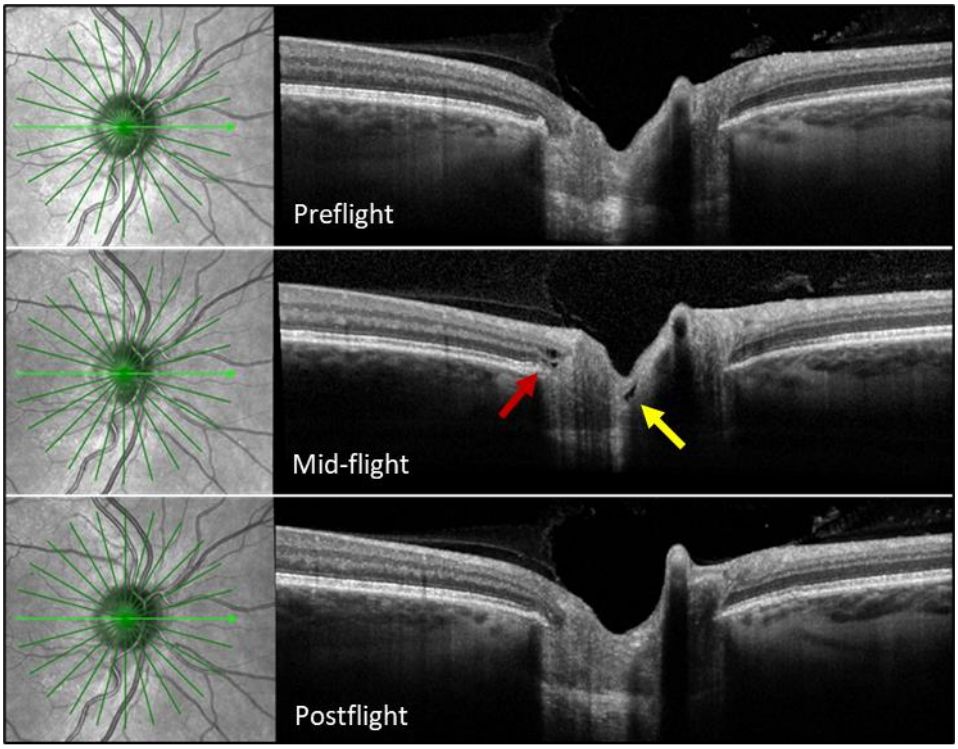

Figure 7. *Preflight, inflight, and postflight optical coherence tomography (OCT) images illustrating the development of intraretinal and optic nerve head cysts (red and yellow arrow, respectively) in a crewmember of a long-duration spaceflight. The cysts resolved without medical intervention within 2 months after return to Earth. (Image courtesy from NASA Lifetime Surveillance of Astronaut Health)*

Retinal PEDs represent a separation of the RPE basement membrane from the underlying BM. Terrestrially, retinal PEDs are associated with chorioretinal diseases such as central serous chorioretinopathy and age-related macular degeneration, and with painless blurred vision and/or vision loss when located centrally. In-flight retinal PEDs tend to develop outside of the macula and sit above choroid that has thickened during spaceflight (pachychoroid). Preflight OCT images verify that these defects typically develop in preexisting areas of disrupted RPE. In one case, the retinal PED was detected immediately before the spaceflight, but progressively worsened during the flight (Crewmember A, **Figure 8**). Retinal PEDs often expand vertically during spaceflight, but so far, none have expanded horizontally. Most cases quickly resolve in the months after spaceflight without medical intervention; however, one case progressed into serous chorioretinopathy (non-central) that later resolved without treatment. To date, no retinal PED has affected a crewmember's vision during or after spaceflight. **Figure 8** illustrates the progression of retinal PEDs in 2 crewmembers before, during, and after LDSF on the ISS.

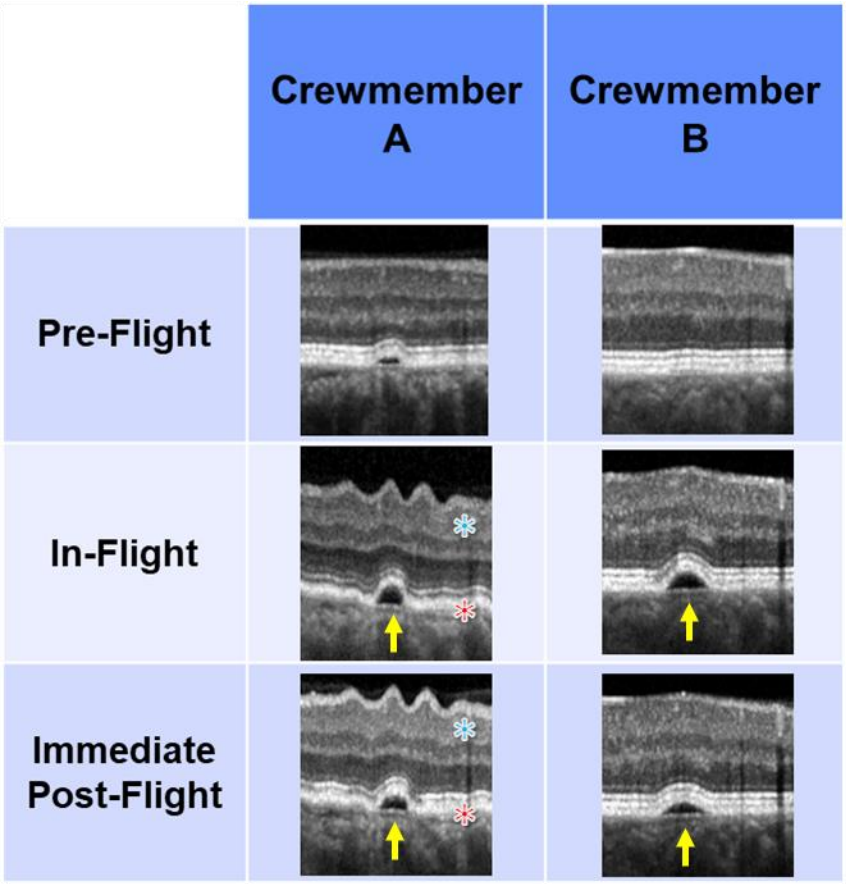

Figure 8. *Cross-sectional preflight, inflight, and postflight optical coherence tomography (OCT) images illustrating the progression of retinal pigment epithelial detachments (PEDs; yellow arrows) in 2 crewmembers (A and B) during long-duration spaceflight on the International Space Station. These defects typically develop in preexisting (preflight) areas of disrupted retinal pigment epithelium (RPE), expand vertically during spaceflight, and then resolve without medical intervention in the months after spaceflight. Note that crewmember A also developed retinal (blue asterisk) and choroidal folds (red asterisk) during the mission. Images courtesy of NASA, Lifetime Surveillance of Astronaut Health.*

Retinal Hemorrhages and Vascular Changes

Superficial retinal hemorrhages have also been detected during LDSF or immediately after flight in a small number of crewmembers ($n < 5$) (Mader et al. 2011, 2017; Macias et al. 2021). Due to their location within the RNFL, these hemorrhages assume a "flame shaped" appearance. In 2 of these cases, the hemorrhages formed alongside retinal ischemia (i.e., CWS). Terrestrially, superficial retinal hemorrhages occur due to a pathology of the superficial retinal capillary plexus, and they are typically associated with systemic conditions such as poorly controlled hypertension, blood dyscrasias, and anemias, none of which are observed in the active astronaut population. Although not a common diagnosis in deployed crewmembers, retinal hemorrhages represent an underlying pathology and are therefore carefully monitored.

Decreases in retinal microvasculature after spaceflight were recently reported in 11/16 eyes of 8 crewmembers completing 6-month missions to the ISS using NASA's VESsel GENeration Analysis (VESGEN) software; decreases in length density were observed in small, but not large, vessels, and the individual with the greatest increase in TRT after spaceflight demonstrated the greatest decreases in vasculature (Vyas et al. 2020; Lagatuz et al. 2021). Another recent study reported that vasculature may be altered differently after LDSF compared with after 70 days of HDTBR (Taibbi et al. 2021); however, this study did not utilize strict HDTBR (i.e., the model that replicates SANS findings), and VESGEN Analysis has not been validated for use on infrared images as used in this study. New techniques, such as OCT combined with line-scanning Doppler flowmetry, can allow for semi-quantitative visualization of retinal and choroidal

blood flow and may provide insights into changes in retinal vascular function during LDSF (Mujat et al. 2019). Additional investigations of changes to retinal vasculature during and after spaceflight, using modalities such as OCT angiography and dynamic vessel analysis, are ongoing.

Optic Nerve Tortuosity (ONT)

ONT has been reported subjectively in ~47% of astronauts after LDSF (Scott et al. 2020). As with GF, objective and subjective analysis techniques exist to assess ONT changes using MRI. Scott and colleagues published a review of the techniques used to assess ONT as degree of change over time from a horizontal and vertical perspective, defined as the congruency of the optic nerve in several coronal sections and the dilation of the surrounding subarachnoid space (Armstrong et al. 2007; Scott et al. 2020). Objective and subjective MRI assessments of ONT differ in slice sizes and type of scan. Subjective assessment of ONT uses T2-weighted coronal, axial, and sagittal scans with 2-3 mm slices (Armstrong et al. 2007), whereas one quantitative approach scores the ONT using T1-weighted 1 mm sagittal slices by capturing the optic chiasm to the globe (Ji et al. 2013) and a second quantitative approach uses axial T1 and T2 scans, coronal T1, and coronal short tau inversion recovery (STIR) images at 3-4 mm slices (Özel et al. 2018). The ONT or kinking that has been reported in some astronauts after LDSF is thought to be due to the cephalad fluid shift and/or change in ICP. To objectively assess whether spaceflight caused increased tortuosity or kinking along the optic nerve and nerve sheath, Rohr and colleagues quantified optic nerve deviation based on the maximum deviation from a centerline path through the optic nerve and reported no statistically significant change in a cohort of 10 astronauts (16 eyes) (Rohr et al. 2020). Although this measure has not been obtained in all of the most severe SANS cases, it suggests that a strong positive association does not exist between SANS and tortuosity development.

Brain Structure

NASA acquires brain and ocular MRI scans before (~18 to 21 months) and after (~ 3 days) LDSF missions as part of the USOS astronauts' medical monitoring. Since the 2017 SANS Evidence Report, several MRI-based studies of astronauts and cosmonauts have reported various structural changes in the intracranial space.

Previous versions of the evidence report noted MRI-based studies documenting metrics related to GF, ONSD distention, and CSF flow dynamics. GF and ONSD changes in astronauts were interpreted as similar to terrestrial IIH patients (Kramer et al. 2012). Concerning CSF dynamics, the findings suggest that spaceflight induces a down regulation of CSF production in response to a cephalad fluid shift, which reverses after return to Earth. Finally, Kramer and colleagues further hypothesized that the maximum systolic velocity of the CSF represents a marker of compensatory reserve and craniospinal compliance (Kramer et al. 2015).

In 2016, Koppelmans and colleagues reported results from a retrospective review of 27 astronaut MRIs (14 LDSF and 13 SDSF, 2 with no prior space flight experience) evaluating brain structural plasticity with spaceflight (Koppelmans et al. 2016). The authors noted that gray matter decreases in the frontal and temporal areas, around the orbits, and in bilateral medial parts of Crus II of the cerebellum. Changes to some regions were significantly greater after LDSF than after SDSF. Overall, no significant changes were found in global gray matter, white matter, CSF, or total intracranial volume.

In a correspondence to the editor, Van Ombergen and colleagues reported changes in brain tissue volume in cosmonauts as compared to values in a ground-based control group (Van Ombergen et al. 2018). This study reported reductions in the volume of gray matter in the orbitofrontal and temporal

cortexes, with no changes in global gray matter or white matter. In addition, CSF spaces along the ventral surface of the brain and ventricles increased after spaceflight, whereas CSF volume below the vertex decreased. Seven months after flight, most changes in gray matter had recovered to preflight levels, whereas the CSF volume in the subarachnoid space continued to increase, suggesting a possible persistent disturbance of CSF circulation.

In 2017, Roberts and colleagues reported MRI based findings of 34 astronauts (18 long-duration and 16 short-duration flights, 28 men) (Roberts et al. 2017). Most notable among the findings include narrowing of the CSF spaces (central sulcus, supervermian cistern, calcarine sulcus), increased total volume of the ventricular system, and an upward shift of the brain within the calvarium. The authors reported that changes occurred more frequently in long-duration flyers than in individuals that flew only short duration flights. Clinical relevance of these findings includes the possibility that narrowed venous sinuses may result in reduced CSF outflow. This narrowing could be due to relative movement of the cranial contents towards the vertex due to lack of a gravitational vector pulling brain contents toward the feet, as occurs in terrestrial (1g) bound humans that are either standing or sitting up. This shift of contents could have several consequences, most of which point toward higher ICP than is normally experienced while on Earth. However, all astronauts showed an upward brain shift, while only 3 presented with ODE based on fundus imaging, and the authors noted that "the relationship between findings on MRI of the brain and [SANS] was inconsistent".

Increased ventricular volumes after LDSF compared to preflight values were also noted in a study of cosmonauts (Van Ombergen et al. 2019). This study was partially reported to the New England Journal of Medicine in 2018, and is noted above (Van Ombergen et al. 2018). Although postflight to long-term follow-up indicated that changes in cosmonauts' ventricular volumes trended toward preflight values, control subjects' ventricular volumes actually decreased over the duration of the study. This is an interesting finding in light of studies reporting that ventricular volumes increase with aging (Resnick et al. 2000; Scahill et al. 2003).

Kramer and colleagues (Kramer et al. 2020) reported results from a prospective, longitudinal MRI-based study comparing preflight images to images collected 1, 30, 90, 180, and 360 days after flight, and they also noted increased ventricular volumes immediately after spaceflight that only partially recovered and remained above baseline 1 year after return to Earth. The authors also reported that spaceflight augmented CSF hydrodynamics including increased CSF aqueductal stroke volume and peak-to-peak CSF velocity magnitude, as well as increased summated brain and CSF volume, white matter volume, and pituitary deformation in 6 of 11 crewmembers. The results suggest that LDSF may be associated with progressive elevations in mean and pulsatile ICP and altered cranio-spinal compliance.

The relationship between spaceflight-induced changes in brain and ocular structure is of notable interest and could allude to independent or shared etiological mechanisms and underlying factors. Roberts and colleagues reported that astronauts presenting with SANS (n=7, defined as the subjective development of ODE as determined by fundoscopy or the presence of choroidal folds) had smaller percent changes in ventricular volume compared to the astronauts without SANS findings (n=11) (Roberts et al. 2021), which was similar to a study of fewer subjects using the same analysis approach (Roberts et al. 2019). Conversely, in 19 astronauts with signs of SANS determined by change in TRT—an objective, continuously scaled measure of ODE—and change in lateral ventricular volume determined by absolute change instead of a percent change, a small positive association existed between these variables (Marshall-Goebel et al. 2021a). It is unclear if the different methods used to quantify the association between ocular and brain findings is the cause for these opposed findings, and further work is needed to clarify if and how these neuro-ocular findings are related. Importantly, astronauts' ventricular volumes after flight appear to be similar to volumes in healthy similar aged individuals, and changes did not reach

levels observed in terrestrial diseases (Marshall-Goebel et al. 2021a). It remains to be determined if the small volumetric changes in the intracranial compartment that have been reported after flight in both astronauts and cosmonauts contribute to any clinical health implications.

Our understanding of how mission duration affects brain structure is limited due to the small number of crewmembers who have completed 1-year long spaceflight missions. Significant changes to the structure of the brain have not been detected after SDSF (~14 days), but rather are associated with LDSF (~6 months). A report of 2 subjects who completed 12-month spaceflight missions determined that one subject had a larger change in ventricular volume than a cohort of crewmembers who completed 6-month missions, whereas the second 1-year mission subject did not (Hupfeld et al. 2020). Furthermore, 3 crewmembers who flew 9-12 month missions did not have a greater magnitude of ventricular volume enlargement than crewmembers of 6-month missions (Marshall-Goebel et al. 2021a). Prospective studies are planned to determine how mission duration affects the development of brain structural changes, and if the brain and ocular structural changes result from a common stressor or if they directly influence each other.

Human Terrestrial Evidence

Head-Down Tilt Bed Rest (HDTBR) Evidence

In comparison to studies of SANS performed on the ISS, studies using spaceflight analogs on Earth typically allow for larger sample sizes, more data collected per subject, broader testing capabilities (e.g., MRI), and substantially lower financial costs. Although no current analog perfectly mimics the weightless environment of space, HDTBR offers an opportunity to explore how human physiology adapts to the sustained unloading of vertical (Gz) gravitational force (Hargens and Vico 2016). HDTBR induces a chronic headward fluid shift and has been used since the 1970s to investigate how immobility and fluid shifts affect different body systems and to develop countermeasures against these effects (Pavy-Le Traon et al. 2007). Thought to most closely approximate spaceflight conditions, a head-down tilt of 6° was selected as the international standard for HTDBR, and this technique has been further formalized for spaceflight research (e.g., study durations, subject selection criteria, nutritional intake, ethics) (Sundblad et al. 2014, 2016).

After the first report of SANS in 2011 (Mader et al. 2011), subjects participating in 6° HDTBR were monitored for changes in ocular structure. No SANS findings were observed during the initial study in which subjects were exposed to 70 days of 6° HDTBR (Taibbi et al. 2016). However, a subsequent report published in 2017 suggested that the use of a standard pillow under the head during HDTBR was sufficient to re-introduce the hydrostatic pressure gradient and reduce ICP by 4 mmHg (Lawley et al. 2017). Given that one or more pillows were typically used during HDTBR and subjects would often raise their upper body onto a forearm to eat meals, it was hypothesized that bed rest subjects were inadvertently countering the headward fluid shift to a level that was sufficient to prevent the development of SANS findings. Shortly thereafter, a “strict” 6° HDTBR paradigm was implemented that precludes supporting the head with a traditional pillow in the supine posture and propping on an elbow for any purpose (Laurie et al. 2020a); only a specialized head and neck support for side sleeping that does not perturb the 6° HDTBR posture was permitted. This new “strict” 6° HDTBR model has been used twice to date and has induced subtle signs of ODE in healthy test subjects (Laurie et al. 2020b, 2021). In the first strict head-down tilt (HDT) study (Laurie et al. 2019), Frisén grade 1 or 2 ODE developed in 5 of 11 (45%) subjects, and retinal

thickening was greater than that which had been previously reported by Taibbi when "strict" HDT was not implemented and optic disc edema did not develop (Taibbi et al. 2016).

During the initial strict HDTBR study, ODE developed within the first ~2 weeks of strict HDTBR exposure, as quantified by the change in TRT (Laurie et al. 2020b). Eight of 11 (73%) subjects had increases in TRT from the pre-HDTBR baseline (supine) that suggested development of the earliest signs of ODE (Laurie et al. 2020b). The average increase in TRT was 36 µm at HDTBR day 15 and 54 µm at HDTBR day 30 (Laurie et al. 2020b). Although mildly elevated ambient CO_2 (~4 mmHg) was implemented in the study design to simulate levels similar to those on ISS (Law et al. 2014), a separate study later documented evidence of ODE in 18 of 24 (75%) healthy subjects undergoing strict 6° HDTBR for 60 days in an environment without any added CO_2, serving as the ideal control condition (Laurie et al. 2021). The 8 participants in the latter study who were exposed to HDTBR without a countermeasure had an average TRT increase of 21 µm at HDTBR day 15 and 37 µm at HDTBR day 58 (**Figure 9**). Circumpapillary RNFL thickness remained at normal levels throughout this study, further indicating that the ODE was mild (Laurie et al. 2021), similar to the ODE that develops in crewmembers. Although the proportion of participants with increased TRT were similar across the 2 studies, the data collected in the normocapnic environment confirmed that strict 6° HDTBR, alone, is sufficient to initiate the development of ODE (Laurie et al. 2021). Furthermore, the onset latency and magnitude of changes in TRT in the second study are consistent with observations made during spaceflight, and as with astronauts who have returned to Earth, the resolution of elevated TRT occurred gradually after both of the strict HDTBR studies (Laurie et al. 2020b, 2021; Macias et al. 2020).

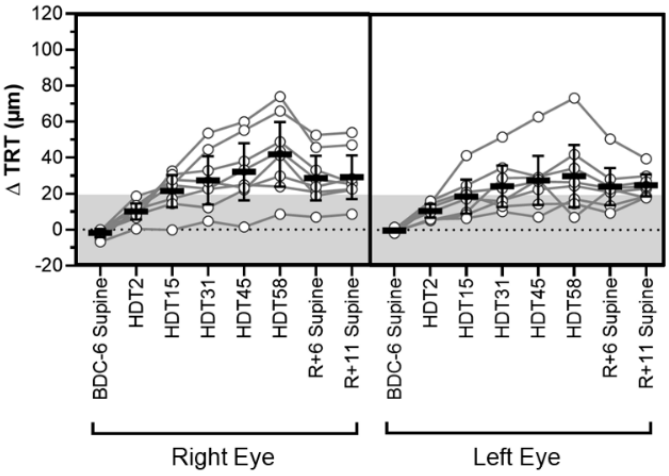

***Figure 9**. Total retinal thickness (TRT) increases during head-down tilt bedrest (HDTBR). Compared to the seated baseline measurement, TRT increased in the right and left eyes of healthy subjects (n=8) who completed 60-days of strict 6° HDTBR in a normocapnic environment. These subjects composed the control arm (i.e., no countermeasure) of the artificial gravity bed rest with the European Space Agency (AGBRESA) Study. Circles represent individual subject data points, gray lines connect for individual subjects, horizontal bars represent the mean across subjects, error bars represent the 95% CI, and the gray region represents the ±19.4 µm measurement variability threshold. BDC, baseline data collection; HDT, head-down tilt; R, recovery. Adapted from Laurie, et al.* Physiological Reports, *2021.*

Chorioretinal folds have also been shown to develop during strict 6° HDTBR (Laurie et al. 2021). OCT analysis of the retina revealed that 6 of 24 (25%) subjects who participated in the abovementioned 60-day bed rest study developed choroidal folds, retinal folds, and/or peripapillary wrinkles. Chorioretinal folds developed in the control group (i.e., HDTBR with no countermeasure) and in the groups that were exposed daily to 30 minutes of either continuous (cAG) or intermittent (iAG) artificial gravity via centrifugation during HDTBR. Across the 3 groups, 4 subjects developed a single type of fold, one subject developed choroidal and retinal folds in one eye, one subject developed all 3 types of folds in one eye,

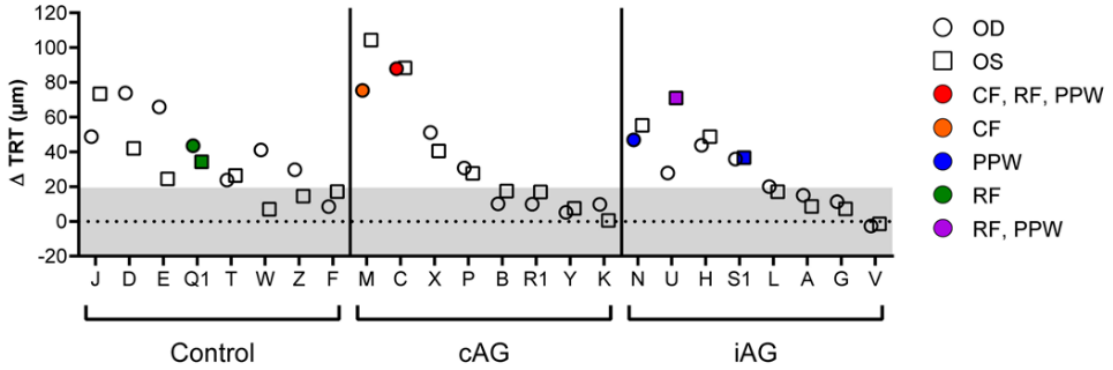

***Figure 10**. Chorioretinal folds can develop during strict 6° head-down tilt bed rest (HDTBR). Three types of chorioretinal folds were observed during 60 days of strict 6° HDTBR with or without a 30-minute daily exposure to artificial gravity: choroidal folds, retinal folds, and peripapillary wrinkles. Four subjects developed only one type of fold, one subject developed choroidal and retinal folds in one eye, one subject developed all 3 fold types in one eye, and one subject developed bilateral retinal folds. All retinas that formed chorioretinal folds also had increases in total retinal thickness that exceed the modeled measurement variability (gray). Circles/OD, right eye; squares/OS, left eye; cAG, continuous artificial gravity; iAG, intermittent artificial gravity; CF, choroidal folds; RF, retinal folds; PPW, peripapillary wrinkles. Adapted from Laurie, et al.* Physiological Reports, *2021.*

and one subject developed bilateral retinal folds. All chorioretinal folds persisted for at least 11 days after HDTBR, except for one eye in which peripapillary wrinkles resolved. Chorioretinal folds formed only in retinas that had signs of early ODE, and all of these retinas had a change in TRT that exceeded 24 µm (**Figure 10**). IOP did not decrease with strict HDTBR, therefore, hypotony does not appear to have facilitated the documented fold formation. As mentioned above in the *Chorioretinal Folds* section, it has been hypothesized that the anterior expansion of the choroid during spaceflight contributes to fold formation (Friberg 1989). Although no evidence of choroidal thickening was observed in the 60-day HDTBR study (Laurie et al. 2021), a separate study has reported that 3 days of strict 6° HDTBR is sufficient to increase choroid thickness by ~9 µm and that this effect can be attenuated with nightly use of 20 mmHg lower body negative pressure (LBNP) (Lawley et al. 2020). The magnitude of choroidal expansion documented by Lawley and colleagues (Lawley et al. 2021) is less than occurs during spaceflight (Macias et al. 2020). Thus far, other ocular findings associated with spaceflight, such as decreased axial length and changes in visual acuity (attributed to a change in refractive error), have not been observed with strict 6° HDTBR (Laurie et al. 2021).

Acute Head-Down Tilt Evidence

Whereas the development of a spaceflight analog that induces some SANS findings is a major step forward in our ability to study mechanisms and potential countermeasures for SANS, studies on a shorter acute timescale also provide meaningful data and evidence that will help broaden facets of our understanding of SANS. For example, posture changes between prone and supine positions allow for assessments of the eye in which the anterior-posterior gravitational gradient can be altered (Anderson et al. 2017). Given the mild elevations in ambient CO_2 on the ISS, simulating this physiologic stressor in combination with a headward fluid shift may determine if the effects of these stressors interact. Acute inspiration of mildly elevated levels of CO_2 suggests that breathing up to 1% CO_2 is unlikely to have a physiological consequence, even during an acute headward fluid shift due to 6˚ HDT (Laurie et al. 2017).

During exposure to 12˚ HDT for up to 26 hours, the addition of 0.5% CO_2 to the ambient air did not affect blood volume or internal jugular vein (IJV) cross sectional area (Marshall-Goebel et al. 2018).

Modeling Evidence

Establishing boundary conditions for how ocular tissues respond to various pressures and/or flows could provide insight into how individual anatomical variability could explain the variability in SANS findings among crewmembers. Strain, stress, and stiffness of ocular tissues may play a role in the biomechanics of the ONH. Ocular geometry and material properties of the tissue may contribute to strain and stress of posterior ocular structures, for example at the ONH and the lamina cribrosa (LC). Both IOP and ICP can contribute to these tissue strains and stresses (Feola et al. 2016). Some factors that contribute to the ONH biomechanics are size and shape of the scleral canal, scleral thickness, regional laminar density, and collagen beam orientation. Therefore, eyes with identical IOPs may exhibit different strain fields because of differences in their structural stiffness (Bellezza et al. 2000). Recent work characterized the mechanical behavior of porcine optic nerve sheaths through inflation and axial loading that allowed for unconfined lengthening, twisting, and circumferential distension (Raykin et al. 2017). The authors reported a "cross-over point" in the pressure-diameter curves under varying axial loads and suggested this represented a protective behavior to prevent optic nerve compression.

Finite element modeling suggests that structural deformations at the vitreoretinal interface may not correspond with those at the anterior surface of the LC. In addition, scleral and laminar compliance may contribute more to average strains within the LC than compliance of neural and pia matter tissues (Sigal et al. 2004). Finite element modeling demonstrates that scleral stiffness greatly influences ONH biomechanics (Sigal et al. 2005). The sclera is the primary load-bearing tissue of the eye and is less compliant than other ONH tissues. Alterations in scleral tissue properties can modify how the sclera responds to IOP or other pressures at the posterior of the eye, and therefore the less compliant structures at the ONH can be modified as well. High or heterogenous scleral strains may translate and impact tissues at the ONH, for example, causing alterations in LC structure, compression of axons, and/or reduction in ONH microvascular blood and interstitial fluid flow (Downs et al. 2003). Indeed, modeling work suggests CSF pressure impacts the strain distribution within the LC and the retrolaminar neural tissue (Feola et al. 2017). Further modeling studies have identified choroidal geometry at the insertion to the ONH as a possible factor driving variability in the strains that develop at the prelaminar neural tissue (Feola et al. 2018). Other studies have used lump-parameter models to simulate the headward fluid shift that occurs in weightlessness, and to estimate factors with the greatest effect on IOP and/or ICP (Nelson et al. 2017, 2020). Acute changes in ICP generated by head-down tilt posture have been used to quantify the stiffness of the optic nerve sheath using finite element modeling (Lee et al. 2020a). Although these studies show promise for modeling the acute fluid shift, more experimental data is required to determine the chronic changes that occur during prolonged stays in weightlessness when tissues may change to accommodate to new set points that reduce the overall stress within the system. These studies have resulted in intriguing hypotheses that may help guide future research to understand the interindividual variability in the presentation of ODE. Understanding how these models translate over longer periods of time will be necessary since certain ocular parameters appear to respond to changes in the gravitational vector over the course of 60 min (Anderson et al. 2017).

Potential Contributing Factors

Hydrostatic Fluid Redistribution

In a 1*g* environment, acceleration due to gravity creates a downward force that acts on the body's fluids. Therefore, a hydrostatic pressure gradient exists across the body's axis, resulting in a higher pressure at the lower extremities and lower pressure at the head when in the upright posture. This is most evident in the standing position. The arterial pressure in a standing male of average height has been estimated to be 200 mmHg at the foot and only 70 mmHg at the head (Hargens and Richardson 2009). The venous blood is also subject to the hydrostatic gradient, and gravity assists cerebral venous drainage from the head, preventing cerebral venous congestion. Upon exposure to weightlessness and loss of the hydrostatic gradient, there is a cephalad fluid shift of 1-2 liters from the lower body as fluids redistribute evenly across the body axis. Consequently, arterial and venous pressures across the body's axis equalize, resulting in similar pressures at the foot and the head during spaceflight. Rowell reported that arterial pressure was approximately 98 mmHg at the foot and 99 mmHg at the head when supine (Rowell and Blackmon 1988). Thus, vascular, interstitial, and cerebral spinal fluids move from the lower extremities to the abdomen, thorax, and head on a daily basis on Earth when a person assumes a supine position, for example during sleep.

An indication of the changes in central and cerebral hemodynamics that occur as a result of fluid shifts during spaceflight are illustrated by the terrestrial work of Chapman *et al.* (Chapman et al. 1990) and Hirvonen *et al.* (Hirvonen et al. 1995). Chapman and colleagues (Chapman et al. 1990) inserted intraventricular catheters in a group of normal subjects and measured ICP while tilting subjects at multiple angles. Similarly, Hirvonen and colleagues (Hirvonen et al. 1995) measured central venous pressure (CVP) in normal subjects at similar tilt angles. In the upright position (0 degree), ICP in a representative subject was -2.3 mmHg (-3.1 cm H_2O), while Hirvonen *et al.* found that CVP was 0 mmHg. In the supine position (90 degrees), ICP increased to 9.2 mmHg (12.5 cm H_2O), and CVP increased to 5 mmHg. When subjects were placed in HDT (-30 degrees), ICP increased an additional 14.8 mmHg (20.1 cm H_2O) from the supine position to 24.0 mmHg (32.6 cm H_2O), while CVP in a similarly tilted subject increased to 9 mmHg (12.2 cm H_2O). These invasive experiments document how cephalad fluid shifts affect CVP and ICP. During spaceflight astronauts experience a chronic fluid shift, and there is no ability to reduce CVP or ICP to near zero by standing up during weightlessness.

Intracranial Pressure

The pressure-volume relationship between ICP and volume of CSF, blood, and brain tissue is known as the Monro-Kellie doctrine (Mokri 2001). The cranium's constituents (CSF, blood, and brain tissue) maintain homeostasis, such that any increase in volume of one of the cranial constituents must be compensated for by a decrease in volume of another. However, a small buffering capacity exists for increases in intracranial volume primarily by the volume of CSF, and to a lesser extent, the volume of venous blood. These buffers respond to increases in volume of the remaining intracranial constituents. For example, in a head trauma patient with an expanding epidural hematoma the increased mass will be compensated by the displacement of CSF and venous blood out of the cranium (Mokri 2001).

Invasive direct measurements of ICP have not been conducted during spaceflight, although many of the possible risks specific to obtaining ICP measures during spaceflight have been reviewed (Barr 2014). Lawley and colleagues (Lawley et al. 2017) used patients that had implanted Ommaya reservoirs for central nervous system chemotherapy administration, but who were asymptomatic for at least 1 year, to

directly measure ICP during ~20-second periods of weightlessness achieved during parabolic flight and compared ICP values to those obtained in both seated and supine positions. A fluid-filled 25-gauge needle was inserted into the Ommaya reservoir and attached to a pressure transducer to continuously measure ICP during posture changes and weightlessness during parabolic flight. ICP was 4 ± 1 mmHg while seated and increased to 15 ± 2 mmHg after stabilization in the supine position (Lawley et al. 2017). In a separate experiment, these same subjects were in the supine position throughout parabolic flight and ICP decreased by 3.8 ± 2.9 mmHg after transitioning from 1*g* to 0*g* (Lawley et al. 2017). This indicated that ICP during ~20 sec of weightlessness falls to levels between seated and supine values on Earth. These data led the authors to conclude that removal of the gravitational vector does not raise ICP to pathologically elevated levels.

Before measuring ICP during spaceflight, "normal" levels of ICP must be determined to correctly interpret future results. ICP can be measured with direct insertion of a pressure transducer into the lateral ventricle of the brain, but it is often assessed via lumbar puncture while patients are positioned horizontally on their side. Because of the invasiveness required to access and measure ICP, few reports exist for healthy populations, making interpretation of "normal" exceedingly difficult. A review of the literature and discussions with clinicians have determined that a pressure of 6 to 25 cm H_2O should be considered "normal" (Lee and Lueck 2014). To identify cutoff values for "pathological intracranial hypertension," Bø and colleagues prospectively collected CSF opening pressure values in 339 patients. The mean value was 17.5 cm H_2O, but the range was 4.0 to 30.0 cm H_2O, and their multivariate model suggested male sex, younger age, and higher body mass index were all associated with higher CSF opening pressure values and recommended using a cut-off of 30 cm H_2O for male subjects and 25 cm H_2O for female subjects (Bø and Lundqvist 2020).

A review of medical records from the Mayo Clinic from 1996-2009 provided estimates for ICP in 33,922 patients, although those considered to have pathologically elevated ICP >25 cm H_2O were not included in the analysis. The mean ± standard deviation (SD) for the 20–49-year-old group was 15.6 ± 3.7 cm H_20 (11.5 ± 2.7 mmHg), which was significantly higher than ICP for the 50–59-year-old group of 14.8 ± 3.7 cmH_2O (10.9 ± 2.7 mmHg) (Fleischman et al. 2012). In a smaller cohort of truly healthy volunteers (n=11, 8 women), ICP while supine was a mean ± SD of 10.5 ± 1.5 mmHg (14.3 ± 2.0 cm H_2O) (Eklund et al. 2016); multiple other studies that reported normal supine ICP values were also noted, despite studying patients with various neurological conditions, and values ranged from 11.5 to 20.1 mmHg (15.6 to 27.3 cmH_2O). In addition, the former cancer patients with Ommaya reservoirs who were studied in parabolic flight had mean supine ICP values of 14 to 16 mmHg (19 to 21.8 cm H_2O) (Lawley et al. 2017), whereas 9 neurosurgical patients who were selected with supine ICP < 18 mmHg, did not show a pathological ICP profile during 24 hour recordings, and did not report symptoms such as headache or nausea during tilting had a mean ventricular ICP while supine of 11.6 mmHg (15.8 cm H_2O) (Petersen et al. 2016). Together, these studies reveal the variability in "normal" ICP measurements of healthy individuals and provide the best context for interpreting values obtained in crewmembers before, during, or after spaceflight.

Some have hypothesized that heavy resistance exercise conducted as a countermeasure to muscle and bone loss during LDSF may lead to periodic spikes in ICP, especially in combination with Valsava, and thus contribute to SANS signs and symptoms. The same patients with Ommaya reservoirs performed leg-press exercises during head down tilt (n=4) and during the weightlessness phase of parabolic flight (n=8) while conducting Valsalva and Mueller maneuvers (Lawley et al. 2017). Because of the slight increase in ambient CO_2 on the ISS these subjects were also exposed to 0.7% CO_2 during exercise and throughout 24 hours of 6° head-down tilt. In the supine and 6-degree head down tilt posture (after 5 min and 25 hr), conducting a Valsalva maneuver during leg press contractions led to increases in ICP.

An additional study of subjects with the implanted Ommaya reservoirs assessed the lowering of ICP by reducing CVP with the use of venoconstrictive thigh cuffs (VTC) and an impedance threshold device (ITD) (Hansen et al. 2021). The investigators found that CVP and ICP were both reduced significantly with the use of the ITD by 3 and 4 mmHg, respectively. However, the inflation of the constrictive cuffs to 30 mmHg did not result in a reduction in CVP and only resulted in a minimal reduction in ICP of 1 mmHg (Hansen et al. 2021). It is possible that this level of pressure and the short 2-minute duration were insufficient to adequately sequester venous blood to substantially affect CVP; the one subject with cuffs that were inflated to 50 mmHg had little change in ICP, although that subject started with the lowest ICP of all 4 participants. Whether ICP would have changed further if application were sustained for longer periods of time is unknown. This study suggested that countermeasures to reduce CVP can have a positive effect at reducing ICP, whereas those that fail to reduce CVP have minimal effect on lowering ICP.

Recently, a modeling method using cerebral blood velocity that was obtained from the middle cerebral artery via transcranial doppler, and arterial blood pressure waveforms obtained from the radial artery via tonometry, was used to noninvasively assess ICP in 11 astronauts after spaceflight: (Iwasaki et al. 2021). Measurements were obtained in the supine and seated positions before and after flight (Iwasaki et al. 2021). This study reported that the middle cerebral artery velocity increased significantly after spaceflight, however, noninvasive ICP measures obtained from the modeling method did not change after spaceflight (Iwasaki et al. 2021). The conclusions of the study were that cerebral blood flow was increased, but this did not increase noninvasive estimates of ICP after spaceflight.

As previously mentioned, optic nerve sheath distension has been studied in astronauts, and orbital ultrasound and ocular MRI have been used to assess ONSD expansion. In terrestrial cases of elevated ICP, it is known that optic nerve sheath expansion occurs due to an increase in CSF pressure in the subarachnoid space surrounding the optic nerve, thus resulting in increases in ONSD (Hansen and Helmke 1996). Mader and colleagues analyzed ONSD distension in an astronaut during and after LDSF using orbital ultrasound (Mader et al. 2017). Expansion of the ONSD was later reported in additional astronauts after LDSF (Mader et al. 2021). However, Rohr and colleagues measured ONSD in 10 astronauts using ocular MRI and reported no change after a 6-month spaceflight (Rohr et al. 2020). These data help elucidate the relationship between ICP, ONSD, and the biomechanical factors that may identify some of the interindividual variability in the development of ODE among crewmembers. Additional studies are using ocular MRI to determine the normal variability in ONSD and other metrics over the course of 1 year.

Comparison to Idiopathic Intracranial Hypertension (IIH)

One of the initial hypotheses for SANS proposed by Mader and colleagues (Mader et al. 2011) was that the cephalad fluid shift caused by exposure to microgravity results in a prolonged and pathologically elevated ICP. The primary ocular signs in SANS-affected astronauts after LDSF (i.e., ODE, choroidal folds, GF, and hyperopic shifts) are similar to those seen in the terrestrial IIH condition (Friedman 2007), yet astronauts do not display the classic IIH symptoms such as chronic headaches, diplopia, transient visual obscurations, or pulse-synchronous tinnitus.

IIH, also known as pseudotumor cerebri, is characterized by increased ICP without clinical, laboratory, or radiologic evidence of an intracranial space-occupying lesion, meningeal inflammation, or venous outflow obstruction. This increased ICP can lead to optic disc swelling (papilledema) caused by high CSF pressure in the distal optic nerve sheath, elevation of the pressure in the central retinal vein, and impaired perfusion of the neurons as their axons traverse the LC (Brazis and Lee 1998). Thus, the GF, ONSD distension, and ODE noted in astronauts represent similar findings to those in patients with IIH. However,

the fact that astronauts do not manifest other findings typically associated with IIH supports the possibility of an alternative etiology.

There are similarities between IIH and SANS, but disparities become obvious when their demographics, signs, and symptoms are compared. **Table 1** lists some of the main commonalities and differences between these 2 pathologies. Data on IIH in **Table 1** were obtained from publications associated with the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT). The stereotypical IIH patient is an overweight or obese female of childbearing age, reporting to a medical provider with subjective complaints related to severe headaches, transient visual obscurations, pulsatile tinnitus, and/or sensitivity to light (Wall et al. 2014; Wall 2017). This does not represent the typical deployed spaceflight crewmember who in their late 40s with a normal body mass index; both male and female crewmembers present with SANS signs; and deployed crewmembers do not report headaches consistent with IIH-like symptoms. If symptoms are reported by crewmembers, the complaints are usually related to changes in near visual acuity due to spaceflight-associated GF and the resultant hyperopic shift.

Both IIH and SANS share the hallmark sign of ODE. However, papilledema in IIH is usually more severe by the time patients present with symptoms, spanning across the entire Frisén grading scale (i.e., 0 through 5), with Frisén grade 2 being the most common rating reported in the IIHTT (Wall et al. 2014). In SANS cases, all but a single eye have been Frisén grade 1 or not met the criteria for grade 1. In one instance, one eye of one crewmember was diagnosed as a Frisén grade 3 (Mader et al. 2011).

There are also subtle but distinct differences in ONH anatomy between IIH and SANS cases. IIH grossly displaces the entire ONH forward (anteriorly) due to the force applied by elevated ICP, and IIH patients often exhibit anterior deformations of the peripapillary RPE and BM towards the vitreous (Kupersmith et al. 2011). These deformations are generally not observed in cases of disc edema due to pathologies in which ICP is not elevated, such as anterior ischemic optic neuropathy (Sibony et al. 2011). Furthermore, they have been shown to resolve after ICP is lowered (Sibony et al. 2014), suggesting that the mechanical deformations occur in response to elevated ICP and a decreased translaminar pressure difference (IOP – ICP).

Anterior deformations are often observed in IIH patients with mild disc edema (e.g., Frisén grades 1 and 2) (Pardon et al. 2019), suggesting that changes in RPE/BM shape should also be detectable in SANS if ICP is altered during spaceflight. Patel et al. determined postflight changes in anterior-posterior position of the BMO using the parameter BMO height, defined as the minimum distance from the BMO to a 4 mm RPE reference line centered on the ONH (Patel et al. 2018). The BMO position shifted an average of 9.9 µm posteriorly after return to Earth. This change is not consistent with a decrease in the translaminar pressure difference, as observed in IIH patients, but instead is consistent with an increase in IOP or decrease in ICP. Although an initial increase in IOP occurs on entry into weightlessness (Mader et al. 1993; Draeger et al. 1995), IOP is thought to return to normal levels within a matter of days and appears similar to values in a supine posture throughout LDSF (Greenwald et al. 2021). The posterior displacement of the BMO observed after spaceflight may be due to hydrostatic draining (i.e., ICP reduction) on return to Earth (Patel et al. 2018). Changes in BMO position during spaceflight are currently under investigation.

Terrestrial papilledema often induces visual field defects, and therefore, visual field testing can be used to monitor the effectiveness of medical interventions in IIH cases. For these reasons, mild visual field loss was an inclusion criterion for subject recruitment for the IIHTT; IIH patients were required to have a perimetric mean deviation between -2 and -7 dB on 24-2 Swedish Interactive Threshold Algorithm (SITA) Standard visual field testing (Wall et al. 2014). The most common visual field defect encountered in IIHTT subjects is an enlarged blind spot with a partial arcuate defect (Keltner et al. 2014; Wall et al. 2014; Wall 2017). In SANS, visual field defects are rarely diagnosed. Currently, only 2 crewmembers have been

diagnosed with enlarged blind spots immediately after flight, and one other crewmember self-reported an in-flight scotoma that resolved before return to Earth. In all 3 cases, the visual field defects occurred in crewmembers diagnosed with ODE.

Over 95% of IIH patients present with bilateral ocular signs, as the pathology is generated systemically by elevated ICP, rather than locally within the orbit for a particular eye. Historically, there were some anecdotal reports that SANS was biased towards the right eye. This observation was based on subjective testing (fundoscopy in particular), where gross signs of SANS were detected either in the right eye only or found to be more significant in the right eye than the left. In more recent years—especially since the application of objective OCT technology—less evidence supports a true right-side bias in SANS. TRT data from OCT images provide a quantification of ODE and demonstrate close agreement between eyes. The change in TRT at FD120 was not statistically different between eyes, with a mean ± SD difference between eyes of 8 ± 13 µm (n = 11 pair of eyes, P = 0.0662) (Macias et al. 2021).

Subjects in the IIHTT had elevated ICP, as was expected, averaging 34.4 cm H_2O and ranging from 21 to 67 cm H_2O (Wall et al. 2014). ICP testing is not routinely performed by NASA, and so these data are limited for astronauts. A postflight lumbar puncture has been performed on fewer than 10 crewmembers, all due to the development of Frisén grade ODE during LDSF. It is important to note that no pre-flight ICP data are available for these crewmembers, and no ICP data are available for any crewmembers who did not develop SANS. For this very limited dataset, the postflight ICP ranged from 18 to 28.5 cm H_2O. Thus, there is a continued need to prospectively measure ICP before, during, and after spaceflight in those with and without ODE before definitive statements can be made about the role of pathologically elevated ICP in SANS pathogenesis.

Both IIH and SANS cases can present with similar MRI findings, such as GF, optic nerve sheath distention, increased ONT, ONH protrusion, and an empty sella (Degnan and Levy 2011; Kramer et al. 2012). In contrast, when comparing MRIs taken before and after spaceflight, the brain of LDSF crewmembers has been reported to displace upward in the calvarium, the central sulcus narrows, and the lateral ventricles enlarge by ~10-15% (Roberts et al. 2017; Van Ombergen et al. 2018), whereas IIH patients can have slit-like ventricles (Roberts and Petersen 2019). Although these brain changes (i.e., upward displacement, narrowing of the central sulcus, and enlargement of the lateral ventricles) have been observed after spaceflight, a definitive relationship with other SANS findings continues to be investigated.

Table 1. *Comparisons of the general demographics, signs, and symptoms of terrestrial idiopathic intracranial hypertension (IIH) and Spaceflight Associated Neuro-ocular Syndrome (SANS).*

	Idiopathic Intracranial Hypertension (IIH)	**Spaceflight Associated Neuro-ocular Syndrome (SANS)**
Sex	≥ 90% female	Unresolved. Diagnosed in males and females, contrary to previous reports suggesting a male-only condition
Body Mass	100% overweight; 88% obese (Wall et al. 2014)	Normal
Symptoms	Headache (84%); transient vision obscurations (69%); pulsatile tinnitus (52%); photophobia (48%); diplopia (18%) (Wall 2017)	Near vision complaints (reported by 48% of astronauts during long-duration missions) (Mader et al. 2011)
Optic Disc Edema	Frisén grades 0-5; grade 2 most common (Wall et al. 2014)	Frisén grades 0-3; grades 0-1 most common

Optic Disc Anatomy	Gross anterior displacement, with bowing of Bruch's membrane opening (BMO) towards vitreous	General expansion, with bowing of BMO away from vitreous (Patel et al. 2018)
Visual Field Defects	Typically presents with enlarged blind spot and partial arcuate defect (Wall et al. 2014; Wall 2017; Keltner et al. 2014)	Rare. Enlarged blind spots diagnosed post-flight in 2 asymptomatic long-duration crewmembers. One scotoma reported in-flight, but resolved prior to landing
Side Bias (Ocular)	> 95% bilateral	OCT data suggests bilateral involvement in most cases, contrary to previous reports of a potential right-side bias
Intracranial Pressure	Elevated. Average 34.4 ± 8.7 cm H_2O; range: 21.0-67.0 cm H_2O) (Wall et al. 2014)	Unresolved. Data limited (n < 10 and collected post-flight due to presence of optic disc edema) Range: 18-28.5 cm H_2O
Magnetic Resonance Imaging – Common Findings	Posterior globe flattening, optic nerve sheath distention, empty sella, increased optic nerve tortuosity, optic nerve head protrusion(Degnan and Levy 2011; Kramer et al. 2012)	
	Brain usually appears normal or shows slit-like ventricles(Roberts et al. 2019)	Brain displaces upward in calvarium; narrowing of central sulcus; lateral ventricles enlarge (Roberts et al. 2017; Alperin and Bagci 2018; Van Ombergen et al. 2018, 2019; Kramer et al. 2020; Hupfeld et al. 2020)

**Brain changes associated with long-duration spaceflight; no definitive association with SANS has yet been established.*

Circulatory System Adaptations

Venous Congestion

A leading hypothesis suggests that SANS findings are caused by the spaceflight-induced chronic headward fluid shift that results in cerebral venous congestion that cannot be reversed or unloaded as on Earth when individuals assume an upright posture. Research into the role of venous congestion has focused on characterizing the headward fluid shift that occurs in weightlessness, but further work is needed to understand why all crewmembers experience the headward fluid shift, yet only a subset develop significant SANS findings. During spaceflight, the IJV cross-sectional area engorges, and pressure increases to a similar degree as occurs in the supine posture on Earth (Marshall-Goebel et al. 2019). Although there is conflicting evidence for the existence of valves in the cerebral venous system, valves have been observed in the superior ophthalmic veins but not in the inferior ophthalmic veins (Zhang and Stringer 2010), thus it is likely that venous volume and pressure is transmitted to the eye. Use of LBNP during spaceflight can redistribute fluid to the splanchnic region and lower limbs. During spaceflight, use of LBNP attenuates the IJV engorgement (Marshall-Goebel et al. 2019) and lowers IOP (Greenwald et al. 2021), suggesting a lowering effect on episcleral venous pressure. Interestingly, chronic weightlessness also induces unique blood flow patterns within the IJV, including reverse flow and blood flow stasis (Marshall-Goebel et al. 2019), although the cause and potential impact of this alteration in flow pattern requires further investigation.

Lymphatic System

Well-regulated lymph function is critical for maintaining normal tissue fluid volume and pressure. The lymphatic system collects excess interstitial fluid and transports this fluid back to the blood through the

thoracic duct (Koh et al. 2005). Distal to the thoracic duct, lymph is pumped against gravity; however, proximal to the duct lymph drains with the help of gravity. Typically, 8 to 12 liters of interstitial fluid are produced daily by transcapillary fluid filtration and transported through the lymphatic vasculature.

Cervical lymphatics in the nasal submucosa at the cribriform plate can absorb CSF (Boulton et al. 1999; Johnston 2003; Koh et al. 2005). In addition, lymphatics around the spinal nerve subarachnoid spaces collect CSF to varying degrees (Koh et al. 2005).

Because lymph pressures are low (0-20 cm H_2O), lymphatic vessels are particularly sensitive to changes in hydrostatic and tissue pressures, which are altered with gravitational changes. It is known that lymphatics from different regions of the body adapt to their regional pressure and flow environments (Gashev et al. 2004). For example, 2 weeks of simulated microgravity in rats causes a potent inhibition of pressure/stretch stimulated pumping in all types of lymphatic vessels (Gashev et al. 2006). The largest inhibition of pump flow occurred in cervical lymphatics during simulated microgravity (Gashev et al. 2006). These lymphatics use cephalic to thoracic hydrostatic pressure gradient to generate lymph flow. Tracer studies suggest that CSF and extracranial lymph compartments are linked physiologically because tracers injected into the cranial CSF later enter lymphatic vessels in the head and neck region (Koh et al. 2005). Animal studies (rat, dog, rabbit, and sheep) demonstrate that a large percentage (50%) of the CSF is cleared by the cervical and extracranial lymphatics (Boulton et al. 1999; Koh et al. 2005). In addition, silicon rubber tracer injected into the subarachnoid space of humans produced extensive infiltration into the lymphatic network adjacent to the extracranial surface of the cribriform plate and optic nerve (Johnston 2003; Koh et al. 2005). An increase in ICP resulted in greater levels of CSF tracer in the optic nerve and deep cervical lymph nodes (McComb et al. 1982). In fact, ligation of the cervical lymphatics results in edema of the brain and protein accumulation (Casley-Smith et al. 1976, 1978). Although there is a clear hypothesis linking the sustained headward fluid shift in weightlessness to possible impacts on lymphatic clearance, what role, if any, impaired lymphatic function has on SANS development remains to be determined. Changes in lymphatic function that develop following actual spaceflight or hind limb unloading, a spaceflight analog, are currently being assessed.

Glymphatic System

As described in the previous report, the central nervous system does not contain traditional lymphatic vasculature; instead, the glymphatic system helps to clear waste from the central nervous system. Recent data demonstrate that CSF moves within the periarterial space, providing a continuous pathway of interstitial fluid exchange (Iliff et al. 2012). Transport of water from the periarterial space into the brain parenchyma is facilitated by aquaporin-4 (AQP4) water channels expressed in the membranes of astrocytes (Iliff et al. 2012, 2013), which "push" the brain parenchyma interstitial fluid into the perivenous space. From this perivenous space, the interstitial fluid can then empty into the cervical lymphatic system (Johnston et al. 2004; Murtha et al. 2014). Moreover, this movement of periarterial CSF into and about the brain parenchyma is associated with movement of solutes to the perivenous sites (Iliff et al. 2012). Data suggest that lipids and lipoproteins greater than 1 kDa are localized to the perivascular space of the brain, and astrocytes release carrier proteins, thus the glymphatic pathway provides a route for lipid distribution.

Rodent data suggest that the glymphatic pathways become enhanced during sleep: volume fraction of interstitial space was 14% during wake and 23% during sleep (Xie et al. 2013). Posture may play an additional role in the glymphatic system's ability to clear waste during sleep. When rats are in the prone position, in which the head is most similar to the upright position and mimicking the awake state posture,

glymphatic transport was in a state of "retention", whereas lateral and supine positions improved glymphatic transport (Lee et al. 2015). In addition, norepinephrine may neuro-modulate the enhancement of the glymphatic system during sleep (Berridge and Waterhouse 2003).

Denniston and Keane proposed that the paravascular system of the retina may be critical in retinal disease (Denniston and Keane 2015). Tracer studies indicate that similar "glymphatic" fluid pathways exist near the paravascular space around the central retinal artery and vein, but not in the lumen of the vessel itself. Sakamoto and colleagues proposed that the fluid communication zone occurs in the paravascular space around the branches of central retinal artery from the subarachnoid space to the optic nerve at the internal limiting membrane (Sakamoto et al. 2010). It remains unclear how this communication zone could be disrupted during spaceflight, however, the translaminar pressure gradient and associated forces on this region may impact fluid communication from the retina to the optic nerve.

In a more recent rodent study, the clearance of beta-amyloid from the retina and vitreous via the ocular glymphatic system was assessed using tracers (Wang et al. 2020). It was found that the beta-amyloid was cleared via the perivenous space and into the lymphatic vessels. Wang and colleagues manually controlled the ICP measurement in the rodents and identified a greater clearance of beta-amyloid tracer through the optic nerve with a decrease in ICP and the converse affect with the increase of ICP (Wang et al. 2020). These results show that the change in translaminar pressure difference drives the ocular glymphatic system outflow in rodents lacking a LC.

Based on recent rodent studies, it has been hypothesized that the cephalad fluid shift in microgravity may inhibit the outflow of the ocular glymphatic system, thereby contributing to the development of SANS findings (Wostyn and De Deyn 2018; Wostyn et al. 2020, 2021). Currently, it is not possible to make invasive measurements in humans to test these hypotheses and no human data are currently available. Furthermore, the data that have led to this hypothesis come from rodents that lack a LC. In humans, the LC microstructure is constructed of collagenous beams in varying orientation and density that respond to mechanical stress and strain from changes in IOP and ICP. It is known that the LC remodels with age, disease, and the acting mechanical forces. The rodent studies performed cannot demonstrate the same mechanical forces acting on the human LC because rodents lack a collagenous LC. It is likely that there are additional factors that would impact the ocular glymphatic system in a human or nonhuman primate, including LC thickness, density of the laminar beams, and a structure of the laminar beams. Yet, the rodent data led to a hypothesis that the swelling at the ONH due to CSF influx could result in glymphatic stasis and lead to the development of ODE associated with SANS and LDSF (Wostyn and De Deyn 2018; Wostyn et al. 2020, 2021). Because of the lack of human data, it remains to be determined if and how spaceflight-induced glymphatic dysfunction may play a role in the spaceflight-induced ODE.

Factors Related to Individual Variability

1-Carbon Metabolism

Smith, Zwart, and others have put forward the theory that the incidence of ophthalmic issues is genetically predisposed (Zwart et al. 2017). This is based on initial findings related to differences in 1-carbon pathway biochemistry between crewmembers. In their initial paper, Zwart and colleagues (Zwart et al. 2012) identified differences in circulating concentrations of the folate and B12-dependent 1-carbon metabolic pathway between astronauts on ISS missions of 48–215 days with (n = 5) and without (n = 15) ophthalmic changes. They found that serum homocysteine (Hcy), cystathionine, 2-methylcitric acid, and methylmalonic acid concentrations were 25-45% higher ($P < 0.001$) in astronauts with ophthalmic changes

than in those without them, and that these differences were present before, during, and after flight. Moreover, preflight serum concentrations of Hcy and cystathionine, and mean in-flight serum folate, were correlated with change (postflight relative to preflight values) in cycloplegic refraction ($P < 0.05$). Zwart and colleagues hypothesized that the higher Hcy may be caused by single-nucleotide polymorphisms of enzymes involved in folate- and vitamin B-12 dependent 1-carbon metabolism (Zwart et al. 2012). In a follow-on investigation, Zwart and colleagues (Zwart et al. 2016) examined whether genetic variations in 1-carbon metabolism genes (methionine synthase reductase [MTRR], methylenetetrahydrofolate reductase [MTHFR], serine hydroxymethyltransferase [SHMT], and cystathionine β-synthase) contributed to susceptibility to ophthalmic changes in 49 astronauts (48 ± 4 years; 58-382 days in space). Results indicated that B-vitamin status and the number of risk alleles of the genes studied were significant predictors of many of the ophthalmic outcomes. Astronauts with the recessive G MTRR 66 allele had a higher risk of choroidal folds and CWS, and those with the SHMT 1420 C allele had a higher risk of ODE after spaceflight. Additionally, preflight dehydroepiandrosterone was positively associated with CWS, and serum testosterone response during flight was associated with refractive change. Furthermore, subjects with 3 or 4 risk alleles who participated in strict HDTBR had greater retinal thickening than those subjects with 0-2 risk alleles (Zwart et al. 2019). Altered 1-carbon metabolism is likely one of many factors during spaceflight that contribute to endothelial dysfunction and vascular permeability that can increase an individual's susceptibility during flight. Animal models have shown that mild hyperhomocysteinemia increases arterial permeability and rigidity, and the blood concentration of folate is lower with a MTHFR polymorphism, promoting an increase in vascular permeability (Symons et al. 2006; Mullick et al. 2006); ultimately, this may result in an increase in ICP. It was recently demonstrated that 35 days of spaceflight disrupts the integrity of the blood brain barrier in mice (Mao et al. 2020), though it is not known whether altered 1-carbon metabolism may exacerbate this effect. Studies are currently underway to investigate a wider array of single nucleotide polymorphisms in the 1-carbon metabolic pathway. In addition, a terrestrial clinical population was identified as having similar characteristics to astronauts with spaceflight-induced ophthalmic issues, and a full characterization of that population is currently being conducted in the hope that this may provide a terrestrial analog population in which to study astronaut ophthalmic issues. Whether these genotypes and resulting biochemical and physiological differences are associated with the mechanisms leading to astronaut ophthalmic issues or whether they constitute genetic markers for other potential genetic associations is unknown and requires further investigation.

Biomarkers

Several potential biomarkers in CSF, and possibly in blood or other body fluids, may in the future be used for early detection of SANS or to identify astronauts with increased risk for developing the syndrome. The panel members of the 2010 Visual Impairment Summit suggested several biomarkers as potential candidates including S-100, platelet count, albumin, C-reactive protein/inflammation markers, insulin-like growth factor, somatostatin, tet-transactivator, myelin basic protein, immunoglobin G index, oligo-clonal bands, atrial natriuretic peptide, vasopressin, and aquaporin. In addition, studies of gene expression profiling, epigenetic modifications of gene expression, proteomics, metabolomics, CO_2 retaining variants, single nucleotide polymorphisms, and copy number variants should be expanded to better characterize individual susceptibility for developing SANS. It has recently been reported that certain microRNAs (miRNAs) are increased in the CSF of IIH patients, and, if also elevated in crewmembers, these miRNAs could potentially be biomarkers that provide insight into the pathophysiology of SANS (Zanello et al.

2018). Currently funded research will collect and analyze CSF samples from crewmembers before and after LDSF. As the etiology of the symptoms is more clearly defined, the appropriate biomarkers will be evaluated.

Anatomical Variations

As discussed throughout this report, the chronic headward fluid shift experienced by all crewmembers during weightlessness represents the most plausible hypothesis for the development of SANS findings during spaceflight. However, because crewmembers present with a range of ocular findings, from clinically relevant ODE with choroidal and retinal folds to no observed changes at all, there must be some other factor, or influencing factor, to explain this wide variability. The previous sections highlighted possible genetic or biochemical factors that could explain this variability, but others have hypothesized individual anatomical factors that may explain those at greater risk for developing SANS. One hypothesis is that loss of tissue weight in microgravity plays a role; one publication documented that preflight body weight was significantly greater in the group who developed ODE or choroidal folds than those that did not (Buckey et al. 2018). It has also been suggested that other anatomical features may play a role in modulating the response to the chronic headward fluid shift at the level of the eye. For example, it has been hypothesized that a small and/or shallow optic cup may predispose an individual to ODE in SANS, whereas a large optic cup may be protective (Stenger et al. 2019). A crowded ONH with small optic cup (i.e., "disc at risk") is a known risk factor for non-arteritic anterior ischemic optic neuropathy and has also been suggested to increase susceptibility to developing papilledema in IIH patients (Geddie et al. 2010; Hamill et al. 2014). Furthermore, ocular biomechanics and tissue properties may be an important factor in the development of SANS, as discussed in the *Modeling Evidence* section above. Future investigations should focus on identifying anatomical features that may predispose certain individuals to developing ODE, or provide protection against developing ODE.

Animal Models

Animal models in research enable the ability to control for genetic factors and allow for tissue harvesting and analysis that is not possible in humans. Unfortunately, efforts to replicate SANS using a murine hindlimb unloading model were not successful in producing findings consistent with SANS (Theriot et al. 2020). In addition, the primary finding of this work suggested a differential response in gene expression within the retina to prolonged hindlimb unloading that may be sex and age-specific. Because SANS affects both sexes and currently there is too little evidence to support any additional risk resulting from age, the ability to interpret or extrapolate these animal data with respect to SANS is limited. Finally, histological analysis revealed photoreceptor loss, choroidal scarring, and retinal pigment epithelium cell migration, with all specimens demonstrating some extent of abnormality. These unfortunate findings further complicate the use of these animal data to inform SANS pathogenesis.

Spaceflight Exposures

Carbon Dioxide

Carbon dioxide constitutes just 0.04% by volume of Earth's atmosphere, resulting in a partial pressure of CO_2 (PCO_2) of 0.3 mmHg at sea level. As a byproduct of metabolic respiration, humans expire CO_2 with each breath, which increases ambient PCO_2 in closed or poorly ventilated environments if not adequately removed. As a result, indoor levels of CO_2 on Earth are typically elevated to ~1 mmHg. The Occupational Safety and Health Administration sets the maximum daily exposure limit for an 8-h work day to a time-

weighted average of 0.5% (3.5 mmHg) (NIOSH 2007) despite the fact that the Environmental Protection Agency recognizes no acute effects for indefinite exposures of up to 1% CO_2 (7.5 mmHg) (Compressed Gas Association 1990). Based on current environmental control and life support systems capability to remove CO_2 from the ambient air, the ISS operational limit for CO_2 is being managed to a 24 hour average of 3 mmHg, and future vehicles are targeting a standard not to exceed 3 mmHg over 1 hour. Measures are currently obtained from monitors attached to the walls throughout the ISS. No published data currently exists demonstrating the exact CO_2 levels experienced by individual crewmembers moving throughout the ISS or during sleep in crew quarters when local pockets of CO_2 may develop.

Elevated arterial PCO_2 leads to vasodilation of cerebral arteries to effectively "wash out" CO_2 from the brain, and augmented ventilation expels CO_2 from the body (Battisti-Charbonney et al. 2011). Although these acute ventilatory and cardiovascular responses are designed to rid the body of excess CO_2, it is unknown if chronic exposure to a mildly elevated CO_2 environment, combined with the headward fluid shift induced by weightlessness, contributes to the structural and functional changes characteristic of SANS. Ambient levels of CO_2 are elevated on ISS because of poor air convection, variable production of CO_2 from up to 6 crewmembers in an enclosed environment, and limitations with currently available hardware designed to remove CO_2. Negative sequelae normally associated with high levels of CO_2 may result from the strong vasodilating effect of CO_2 and include headaches, blurred vision, lethargy, irritability, and neurocognitive deficits. Although these symptoms typically manifest in environments on Earth with high levels of CO_2 (typically greater than 5.0% inspired) (Henning et al. 1990; Law et al. 2014), it is unknown if the chronic exposure to mildly elevated CO_2 (currently ISS is <0.5% CO_2 inspired) experienced by crewmembers on ISS in combination with weightlessness or other spaceflight factors contributes to SANS or contributes to other negative impacts on crew performance, such as reductions in cognitive function (Manzey and Lorenz 1998a, b) or sleep (Barger et al. 2014).

Because air convection is significantly reduced in microgravity, local pockets of CO_2 may develop around the nose and mouth. A computational fluid dynamics analysis revealed that without adequate ventilation, PCO_2 could rise above 9 mmHg within 10 minutes around a sleeping astronaut's mouth and chin (Son et al. 2002). Fans built into the sleep quarters and directed at the astronaut's face are in place to prevent this buildup of CO_2.

Few investigations to date have measured true CO_2 exposures during spaceflight. The Major Constituent Analyzer draws air from fixed locations that may not necessarily reflect local CO_2 levels around astronauts as they move throughout the ISS. Even the portable CO_2 monitors (CDMs) are generally placed on cabin walls and not directly next to the crew, therefore, CDM data may not represent what the crew truly experiences throughout their day. More research is needed to clarify the actual CO_2 exposure experienced by crewmembers throughout the day and during sleep.

As described in more detail in the *Analog Evidence* section above, the spaceflight analog strict 6˚ HDTBR led to the development of ODE in subjects living in an environment with 4 mmHg ambient PCO_2 (Laurie et al. 2019, 2020b). However, given the arterialized and end-tidal PCO_2 measures did not change throughout the course of bed rest, and no other measures (including brain blood flow or cerebrovascular reactivity to CO_2) were altered throughout the study (Laurie et al. 2020a), it appeared that the "strict" nature of the bedrest study was the likely factor leading to ODE and that the ambient CO_2 was likely not a contributing factor. Subjects of a second strict HDTBR study that did not include elevated ambient CO_2 again developed ODE, and chorioretinal folds were observed for the first time (Laurie et al. 2021). These results add further evidence that the mild CO_2 exposure does not play a role in the development of SANS findings. Finally, despite continued efforts to lower the ambient CO_2 levels on ISS, SANS findings continue to emerge in crewmembers during LDSF missions.

What remains unknown, however, is if crew are encountering higher than expected levels of CO_2 due to accumulated pockets when working in areas of poor ventilation or during sleep in confined spaces. If crewmembers are experiencing higher than anticipated increases in arterial CO_2, temporarily causing increases in brain blood flow and consequently ICP, these intermittent stimuli could still be contributing to some of the individual variability in presentation of SANS findings.

Exercise

Exercise is an important countermeasure used to maintain muscle, bone, and cardiac health during spaceflight. Historically, Russian scientists have used a variety of exercise hardware and in-flight exercise protocols during LDSF (up to and beyond 1 year) on board the Mir space station. On the ISS, a combination of resistive and aerobic exercise equipment is used. The functional requirements for physical human performance during each specific phase of Mars and lunar missions, which will include several transitions between gravitational environments, have not been sufficiently defined to determine whether currently developed exercise countermeasures are adequate.

Although resistive exercise on the ISS benefits skeletal morphology and function, its effects on ICP remain controversial. Lawley *et al.* demonstrated an acute increase in ICP during resistive exercise in parabolic flight-induced weightlessness (Lawley et al. 2017). Haykowsky and colleagues invasively examined ICP in fully cooperative, alert, and clinically stable patients who received a ventricular drain as part of their surgical procedure and postoperative care and reported that resistive exercise without a Valsalva maneuver resulted in no change in peak systolic pressure or ICP (Haykowsky et al. 2003). If Valsalva maneuvers are conducted by astronauts during spaceflight, it is possible ICP does increase transiently, but whether these brief fluctuations would be sufficient to contribute to ODE in astronauts is unknown.

In contrast to numerous investigations examining the effects of resistive exercise on cranial pressures, there is a dearth of information regarding the consequences of aerobic exercise on ICP. To our knowledge, the only study that examined ICP during aerobic exercise invasively measured ICP in patients with normal and increased ICP (Brimioulle et al. 1997). Exercise tended to decrease ICP both in patients with intracranial hypertension and in those with normal ICP. The data suggested that because aerobic exercise is generally conducted without Valsalva maneuvers, it is unlikely that ICP will increase during such exercise.

Although more work is needed to determine if exercise during spaceflight plays any role in the development, or possibly prevention, of SANS findings, the observation that strict HDTBR subjects develop ODE and chorioretinal folds despite being completely sedentary suggests any potential ICP change that may occur during exercise is unlikely to be a significant contributing factor. A retrospective review of the amount of resistive versus aerobic exercise performed by crewmembers during spaceflight found no difference between those who did or did not develop SANS (Laurie et al. 2020b).

Diet and Sodium

Sodium, most commonly consumed as dietary sodium chloride (salt), is a required nutrient used in numerous physiological functions, including the regulation of normal distribution of water between the various compartments of the human body (Smith et al. 2015). The Institute of Medicine and the American Heart Association recommend 1500 mg of sodium per day as an adequate intake level (Appel et al. 2011; Susic and Frohlich 2012), however, most of the Western world's population consumes a much higher amount; the average daily sodium intake in the U.S. is more than 3,400 mg (US Dept of Agriculture).

Consumption of excessive salt has been linked to numerous adverse health effects, including hypertension, as well as pressure-independent pathologies such as increased risk for stroke, subclinical cardiovascular disease (left ventricular hypertrophy, ventricular fibrosis, diastolic dysfunction, arterial fibrosis leading to large elastic artery stiffness), fibrotic kidney damage, gastric cancer, and disordered mineral metabolism with increased urinary calcium excretion, potentially leading to osteoporosis. The increased risk of non-pressure related fibrosis is caused by increased oxidative stress and endothelial dysfunction in the setting of high levels of sodium intake, leading to increased mitogenic responses that translate into fibrosis in the heart, kidneys, and arteries (Appel et al. 2011; Susic and Frohlich 2012). An acute increase in sodium intake has been shown to impair vascular endothelial function in young adults with normal blood pressure (Appel et al. 2011; Susic and Frohlich 2012), and middle-aged adults with elevated systolic blood pressure but no other health problems who reduce their sodium intake from moderate levels to less than 1500 mg/d have a reduction in large elastic artery stiffness (Appel et al. 2011). Sodium reduction decreases blood pressure in both normotensive and hypertensive individuals, although the magnitude of this response is still unknown (Appel et al. 2011; Susic and Frohlich 2012).

Foods prepared for spaceflight have always been high in sodium content, a consequence of the food preservation techniques. During the Skylab and Shuttle eras, as well as today in the ISS era, crewmembers have consumed an average of 4-5 grams of sodium daily, and some individuals consume as much a 7-10 grams daily (Smith et al. 2015). Recent efforts at NASA have led to a reduction in the sodium content of many of food items, leading to daily sodium intake of around 3000 mg/d (Lane et al. 2013).

During real and simulated spaceflight, sodium homeostasis and blood sodium levels are maintained (Smith et al. 2015). Over 90% of the dietary sodium is absorbed, so that increased sodium intake leads to an increase in sodium levels in the blood, followed by excretion of the excesses in the urine (Smith et al. 2015). The concern with elevated sodium intake in the context of spaceflight is related to its potential impact on bone health and SANS. More specifically for SANS, the concern is that the sodium will contribute to elevation in arterial blood pressure and to non-pressure related elevations in arterial stiffness. In addition, increased sodium intake may induce an expansion of the extracellular fluid volume, which in combination with weightlessness-induced fluid shifts might further elevate ICP. However, when crewmembers are studied in the days after they return to Earth and are beyond the initial period of re-adaptation to Earth's gravity, no significant change in arterial stiffness is detected (Lee et al. 2020c). Furthermore, blood pressure is either similar to the supine posture on Earth or slightly decreased during LDSF (Norsk 2020), suggesting that any salt retention that results from the diet is not adversely affecting the cardiovascular system and thus SANS development.

A link between increased ICP and altered retention of sodium and water was suggested by a study in which 77% of IIH patients had evidence of peripheral edema and 80% had orthostatic retention of sodium and water (Friedman and Streeten 1998). Impaired saline and water load excretions in the upright posture were noted in IIH patients with orthostatic edema as compared to values from lean and obese controls without IIH. However, the precise mechanisms linking orthostatic changes and IIH were not defined, and many IIH patients do not have these sodium and water abnormalities. Astronauts are well known to have orthostatic intolerance when they return to gravity after LDSF, and the dietary sodium on orbit is also known to be in excess of 5 grams per day in some cases.

SECTION II: RISK IN CONTEXT OF EXPLORATION OPERATIONAL SCENARIOS

The most concerning aspect of SANS is that chronic ODE that does not resolve throughout the duration of an exploration mission could lead to damage of retinal nerve fibers and ultimately uncorrectable vision loss. This has not been observed to date, but the impact of increased mission duration on retinal health remains unknown. Importantly, a need exists to collect SANS-relevant data in crewmembers during and after 1-year spaceflight missions to better determine the impact of mission duration and whether the sustained presence of ODE will ultimately lead to irreversible changes in vision. Additionally, further research is needed to determine the impact of spaceflight on long-term ocular health.

While the exact mechanism leading to the development of SANS findings in some, but not all, crewmembers remains to be fully defined, the leading hypothesis indicates that countermeasures designed to temporarily reverse the chronic headward fluid shift will have the best chance of preventing or reversing SANS. Ground-based evidence suggests that use of moderate levels of LBNP, VTC, and/or inspiratory resistance caused when breathing through an ITD can partially reverse the headward fluid shift (Marshall-Goebel et al. 2021b). Breathing through an ITD, but not donning of thigh cuffs, reduces ICP and CVP (Hansen et al. 2021). Use of moderate levels of LBNP (i.e., 25 mmHg) for up to ~1 hour during LDSF missions partially reverses the headward fluid shift within the cerebral venous compartment, and this effect likely reaches the level of the eye (Marshall-Goebel et al. 2019; Greenwald et al. 2021).

Ongoing effort is needed to translate these preliminary findings from ground-based studies, and acute use studies on ISS, into countermeasure procedures that can be implemented in an operational environment.

Overview of Risk Changes with Exploration Missions

Altered Gravity Environments

All crewmembers who have developed SANS findings during spaceflight have recovered without additional medical intervention after they returned to the gravitational environment of Earth, suggesting that reversal of the sustained headward fluid shift caused by weightlessness is sufficient to treat SANS. It is unknown what level of gravitational gradient is needed to adequately reverse the headward fluid shift. Data collected during partial-gravity exposure induced by parabolic flight suggest that cerebral venous congestion is not reduced until the head-to-foot gravitational gradient exceeds 0.50 g (Lee et al. 2020b).

Mission Duration

The magnitude and duration of ODE in terrestrial patients likely affects damage to retinal nerve fibers, leading to irreversible vision loss. However, because the onset of ODE is often unknown, the duration of mild ODE (e.g., similar in magnitude to that observed to date in astronauts) needed to cause permanent damage is unknown. The results of the Ocular Health Study suggest that ODE can develop within the first month of spaceflight, but the interindividual variability is wide. One crewmember who flew a 1-year long mission had ODE that appeared to plateau in magnitude during the second half of the mission; however, another crewmember first developed signs of ODE late into their 1-year mission (Macias et al. 2021). In

addition, even if the magnitude of ODE does not increase throughout a mission, it is possible that the sustained presence of the edema may still affect retinal function in a time-dependent fashion. Due to the limited number of individuals who have flown ~1 year-long spaceflight missions, the majority of SANS findings have presented during shorter-duration 6-month missions. Any interpretations of the role of mission duration therefore remain premature and require additional research. Future planned research that includes electroretinography measures of retinal ganglion cell function will help inform consequences of mission duration.

Radiation

The space radiation environment in low Earth orbit, where the ISS is located, exposes astronauts to higher levels of radiation than exposures on the surface of the Earth, but the Earth's magnetosphere provides substantial protection even in low Earth orbit. Exploration class missions beyond the protection of Earth's magnetosphere will expose astronauts to greater levels of radiation, in particular greater levels of galactic cosmic radiation (Hassler et al. 2014). Although it is unlikely, crewmembers may also be exposed to even higher doses of radiation during a solar particle event.

Very high levels (20 Gy) of radiation exposure can result in brain edema and neuro-inflammation because these doses of radiation can impair the function of the brain-blood barrier (Yuan et al. 2003, 2006; Bellone et al. 2016), and models suggest this may result in elevated ICP (Lakin et al. 2007). Some mini-pigs exposed to a 2.5 Gy electron simulated solar particle event had higher CSF opening pressures 90-days after exposure (Sanzari et al. 2014). Preliminary data from Sprague-Dawley rats fed an iron-rich diet and exposed to 3 Gy fractionated gamma radiation spread over 16 days (37.5 cGy per day every other day) had greater levels of oxidative stress in the retina and aortic vasculature, suggesting cellular protection mechanisms may be overloaded by the combination of iron load and radiation exposure (Theriot et al. 2016). Published studies that demonstrate radiation induced alteration in blood-brain barrier used radiation doses much higher than those expected to occur during a nominal mission. Therefore, it is unclear if chronic low-dose, low-linear energy transfer radiation can alter the blood brain or retinal barriers and disrupt cognitive and visual function. In addition, it is unclear if high linear energy transfer radiation, the main components of galactic cosmic radiation, affects tissues differently than the low energy transfer radiation radiation typically used in experimental tests on the ground.

Monitoring SANS on Exploration Missions

On Earth, OCT imaging provides the most sensitive measures for detecting ODE or chorioretinal folds (Sibony et al. 2015); a commercial off-the-shelf OCT system has been on the ISS since 2013 (Spectralis OCT1, Heidelberg Engineering) and was upgraded in 2017 (Spectralis OCT2, Heidelberg Engineering). However, the size, mass, and power consumption of this device is too large for exploration missions, and an equivalent device that would enable direct comparisons of data obtained with the OCT1, OCT2, and new smaller device is needed in order to detect SANS progression.

Mechanical SANS Countermeasures

The weightlessness-induced headward fluid shift, relative to the upright position on Earth, that occurs during spaceflight is hypothesized to underlie several physiological consequences of spaceflight including

changes in the cardiovascular and central nervous systems as well as development of the SANS. Thus, SANS countermeasure efforts have concentrated on techniques to reverse the spaceflight-induced headward fluid shift. Notably, LBNP, VTC, inspiratory resistance breathing through an ITD, and artificial gravity via human centrifugation have all been proposed and studied as mechanical fluid shift countermeasures.

LBNP devices, which enclose the lower limbs in a hard casing and are sealed at the top of the iliac crest, are connected to a variable vacuum pump to reduce the pressure inside the chamber to levels lower than atmospheric pressure. The reduced pressure inside the LBNP chamber retains fluid, principally venous blood, in the lower limbs and splanchnic circulation. The physiological effects of LBNP, however, are highly dependent on the amount of negative pressure applied. A higher level LBNP (~30-50 mmHg) is more effective at redistributing and retaining vascular volume in the lower limbs, however, it stresses the cardiovascular system to a much greater degree and can result in a higher incidence of pre-syncope. Thus, high-level LBNP can normally only be tolerated for short durations of time and requires medical monitoring. Because fluid shift countermeasures may have to be implemented for longer durations to be effective as a SANS countermeasure, recent research on LBNP has focused on lower LBNP levels.

Use of 25 mmHg LBNP can decrease IJV area and pressure (Marshall-Goebel et al. 2021b), ONSD (Marshall-Goebel et al. 2017), and cardiac output during application. Notably, LBNP can also decrease ICP in a non-linear, dose-dependent fashion in both the supine and 15° head-down tilt (HDT) postures on Earth while maintaining cerebral perfusion (Petersen et al. 2019b). Of note, LBNP ≤ 30 mmHg decreased ICP ~1-4 mmHg while supine and ~5-8 mmHg while in the 15° HDT position, suggesting that LBNP is more effective at reducing ICP when the starting ICP is higher.

Although the acute effects of LBNP on the cerebral and cardiovascular systems have been researched, the long-term effects of daily application of LBNP are unknown. Because SANS is hypothesized to be due to a mild yet constant increase in ICP and cerebral venous pressure during spaceflight, countermeasure techniques may have to be implemented for multiple hours per day to be effective. Work is ongoing to investigate the feasibility and utility of a mobile LBNP system (Petersen et al. 2019a; Ashari and Hargens 2020), although much has still to be determined before this method can be fully implemented for long periods of time during spaceflight (Harris et al. 2020). Future studies should focus on the efficacy and feasibility of implementing daily LBNP for longer durations, and the efficacy of daily LBNP application on preventing neuro-ocular changes associated with SANS.

Acute use of LBNP on Earth provides insight into those parameters that are rapidly affected by LBNP and thus most likely to be impacted by prolonged use of the countermeasure. When applied to supine subjects on Earth, LBNP appears to provide a more consistent headward fluid shift reversal than VTC or breathing through an inspiratory resistance device (Marshall-Goebel et al. 2021b). However, LBNP is likely the most complex countermeasure to implement during spaceflight, and operational constraints will need to be considered when evaluating the best opportunities to prevent SANS.

As with LBNP devices, VTC aim to sequester blood and fluid volume in the lower limbs. VTCs are placed around an individual's upper thighs and are tightened to reduce venous outflow from the legs (Lindgren et al. 1998). Russian cosmonauts typically wear custom-fitted VTCs, called Braslet-M, in the first weeks of spaceflight to alleviate symptoms of the headward fluid shift, including sinus congestion (Matsnev et al. 1983; Yarmanova et al. 2015). In-flight, use of VTC has been shown to reduce cardiac preload, increase femoral vein cross-sectional area, and reduce IJV area (Herault et al. 2000; Hamilton et al. 2012). In ground based studies using posture changes to induce a headward fluid shift, VTC decreased stroke volume

(Marshall-Goebel et al. 2021b), IJV area (Herault et al. 2000; Hamilton et al. 2012), IOP (Balasubramanian et al. 2018; Marshall-Goebel et al. 2021b), and forehead skin thickness (Diridollou et al. 2001). Contrary to LBNP, which may engage the lumbar CSF space, VTC may not directly influence the distribution of CSF and therefore may not reduce ICP. It is likely that longer durations of VTC use will be required to affect CVP and/or ICP, which may be why no statistically significant change in ICP or CVP was observed after only 2 minutes of use (Hansen et al. 2021). In addition, work is needed to determine the appropriate VTC pressure for use during spaceflight.

LBNP and VTC redistribute fluid volume to the lower limbs continuously, whereas resistive inspiratory breathing through an ITD reduces CVP transiently. With each inspiration, the ITD-induced resistance lowers intrathoracic pressure, thus increasing venous return and decreasing ICP (Convertino et al. 2005, 2011; Rickards 2019; Hansen et al. 2021). Notably, ITD breathing reduces IJV area at end–inspiration and lowers ICP (Kiehna et al. 2013; Metzger et al. 2018; Hansen et al. 2021; Marshall-Goebel et al. 2021b). Breathing through the ITD can be cumbersome and uncomfortable and may not be feasible for extended use. The comfort of the ITD, possible changes in arterial PCO_2 levels resulting from hyperventilation or hypoventilation due to altered breathing patterns, and determination of the prolonged effects on the headward fluid shift would need to be addressed for this countermeasure to be operationally viable and considered as a possible SANS countermeasure.

Although it is still unknown what effect ICP has on the development of SANS findings, some have hypothesized that providing an opposing pressure to ICP at the ONH via increased IOP may represent a novel and simple countermeasure. Intermittent use of swim goggles has been proposed as a way to mildly increase IOP to oppose any changes in ICP (Scott et al. 2019), although it will be important to ensure that the level and duration of IOP elevation does not induce glaucomatous changes to the ONH.

Other SANS Countermeasures

Artificial Gravity

In the artificial gravity bed rest with the European Space Agency (AGBRESA) Study, 2 groups of subjects were exposed to 30 minutes per day of either cAG or iAG via short arm centrifugation that generated ~0.3 g at the eye during 60 days of strict 6° HDTBR (Laurie et al. 2021). The iAG protocol included six 5-minute periods of centrifugation that were separated by 3-minute breaks. The variables tested in the artificial gravity groups were similar to those tested in the control group that was exposed to HDTBR and no centrifugation. Like the control group, both artificial gravity groups had increased peripapillary TRT as compared to pre-bed rest baseline measurements (HDTBR day 58: increase of 35.9 µm for control, 36.5 µm for cAG, 27.6 µm for iAG), and the magnitude of this change did not significantly differ from control for either artificial gravity group. All 3 groups had incidence of chorioretinal fold development (*see* ***Figure 10***). Neither centrifugation paradigm appeared to affect other ocular variables that were not altered by HDTBR in the control group. Further experiments are needed to determine whether a fluid shift reversal of longer duration and/or greater acceleration magnitude at the level of the eye can mitigate the development of ODE and chorioretinal folds during HDTBR.

Pharmaceuticals

The role of elevated ICP in the development of SANS during spaceflight remains unknown. If it is determined that elevated ICP occurs during spaceflight and contributes to the development of SANS

findings, and there is a need to lower ICP in an attempt to improve ocular and/or brain outcomes, then ICP-lowering pharmaceuticals could be considered as a SANS countermeasure. Acetazolamide, a carbonic anhydrase inhibitor, decreases CSF production and is commonly used to lower ICP in terrestrial IIH patients. Acetazolamide has only been used once to treat SANS during the postflight period after LDSF (Mader et al. 2011). The astronaut received acetazolamide (Diamox Sequel) 500 mg daily for 6 weeks, then 250 mg daily for another 2 weeks (total of 2 months). Over that time, the lumbar puncture opening pressure decreased from 28 cm H_2O to 19 cm H_2O, and further treatment was deemed of questionable benefit. It is also noted that in this one case, the individual's urinary creatinine rose from normal to 1.7 g/day, thus enhancing the desire to discontinue the medication. Use of acetazolamide also carries other possible negative side-effects, including lowering IOP, which could negatively impact the translaminar pressure difference and possible worsen ODE. Other common side effects may include fatigue, nausea, diarrhea, vomiting, and paresthesia. This drug is not currently being considered as a countermeasure or treatment for SANS.

Exenatide is a glucagon-like peptide 1 receptor agonist used to manage type 2 diabetes mellitus and for weight loss in obesity through actions in the kidney to reduce Na^+ reabsorption. The glucagon-like peptide 1 receptor is also expressed in the choroid plexus lining the ventricles of the brain, and stimulation of these receptors could reduce secretion of CSF. Use of exenatide in a rat model of intracranial hypertension lowered ICP (Botfield et al. 2017), and a clinical trial is currently underway to assess the efficacy of lowering ICP in patients with raised ICP (International Standard Randomised Controlled Trial Number 12678718). The subjects of this study are being assessed 2 weeks and 12 weeks after twice daily injections of exenatide or placebo to determine ICP, quality of life, and clinical outcome measures. Results from this study have not yet been published. However, this clinical trial is not assessing how effective exenatide is in lowering ICP in individuals that do not have pathologically elevated ICP. If ICP during LDSF is similar to the supine posture on Earth, as occurs during brief periods of weightlessness during parabolic flight (Lawley et al. 2017), then the effectiveness of any ICP-lowering drug would have to be evaluated in individuals with similar ICP levels as occur during spaceflight. Factors such as the baseline ICP during spaceflight, the possible side-effects of an ICP-lowering medication, and the demonstration of decrements of visual functional should be considered before considering use of any ICP-lowering drug during spaceflight as a countermeasure to SANS.

Supplementation with B-vitamins has been hypothesized to lower the risk of developing SANS signs in those with low B-vitamin status or those with single nucleotide polymorphisms that reduce the efficiency of the 1-carbon pathway. Spaceflight and bed rest data document that a B-vitamin-rich metabolic pathway that transfers single carbon units (i.e., the 1-carbon metabolic pathway) may be involved with SANS risk or predisposition. B-vitamin status and the presence of one-carbon pathway single nucleotide polymorphism (SNP) variants predicted the incidence of SANS pathologies, including ODE, in astronauts (Zwart et al. 2016). Specifically, the G allele of MTRR A66G and the C allele of SHMT1 C1420T were associated with incidence of SANS findings (Zwart et al. 2016). Similarly, in a 30 day strict HDTBR study with 0.5% CO_2 exposure, 5 of 11 subjects developed ODE (Laurie et al. 2019) and the same SNPs were associated with a larger increase in total retina thickness and thickening of the RNFL (Zwart et al. 2019).

SNPs of enzymes involved in the 1-carbon pathway and/or low B-vitamin status can affect the efficiency of the pathway, which can in turn affect endothelial function. Stressors related to spaceflight, including a headward fluid shift, can affect endothelial function and also affect the turnover of structural

components of the sclera, making it more susceptible to pathophysiology (Zwart et al. 2019). Vitamin supplementation can serve to overcome genetic hindrances to 1-carbon biochemistry and endothelial dysfunction terrestrially. A spaceflight study is underway to test the effectiveness of a B-vitamin supplement to maximize the function of the 1-carbon pathway and mitigate or prevent SANS in at risk individuals.

SECTION III: DIRECTED ACYCLIC GRAPH (DAG) REVIEW AND INTEGRATION WITH OTHER RISKS

DAG Review: The DAG below (**Figure 11**) highlights potential links to other risks managed by the NASA Human System Risk Board, including the CO_2 Risk, Food and Nutrition Risk, Human-System Integration Architecture Risk, Pharm Risk, and Sleep Risk.

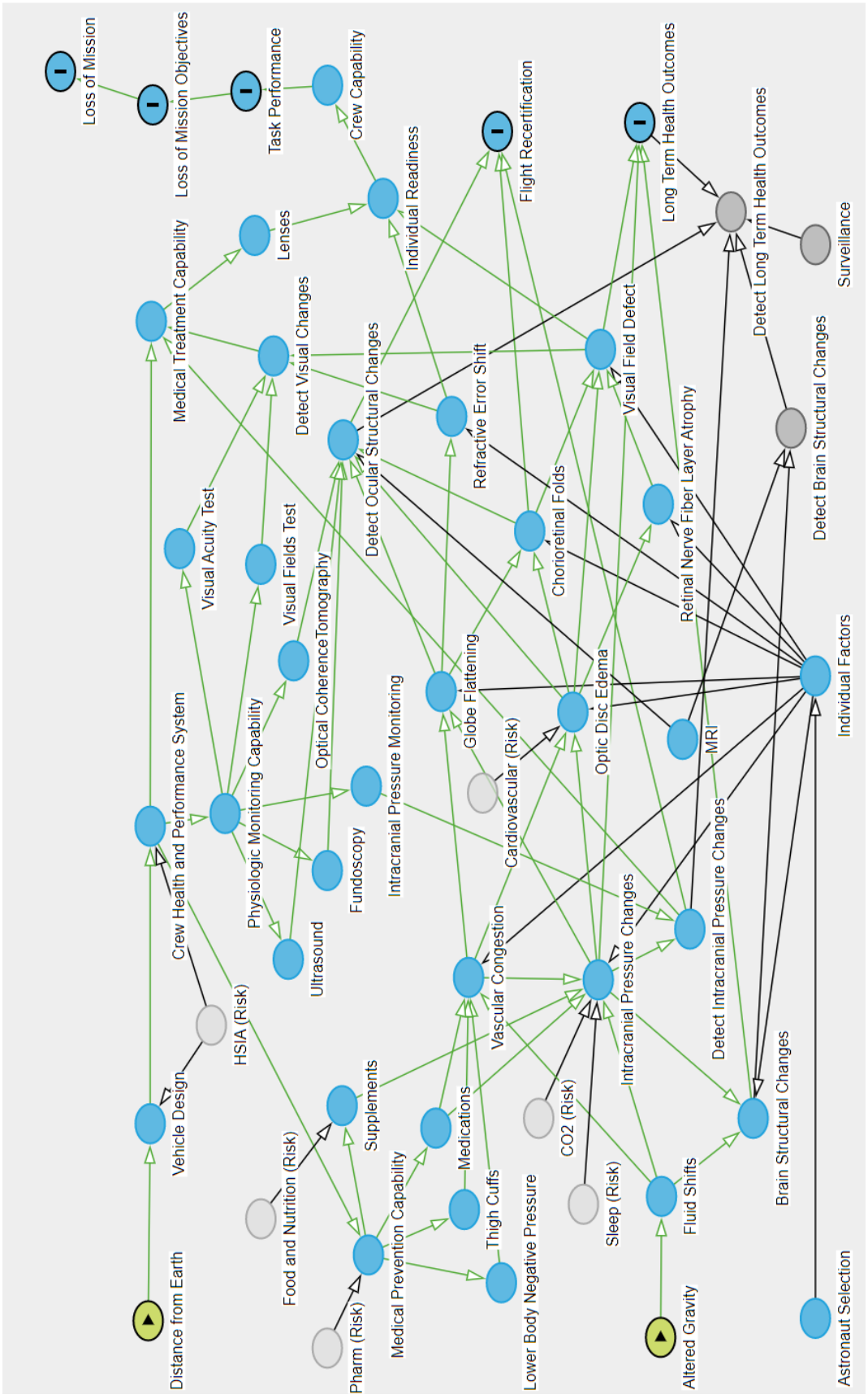

Figure 11. The Directed Acyclic Graph (DAG) linking spaceflight hazards (green nodes, left) to in-mission and post-mission consequences (blue nodes with black vertical bars, right). Blue nodes provide hypothesized and confirmed factors that may explain the development of structural changes during and after spaceflight, and the potential functional outcomes. Yellow nodes in center represent SANS findings. Light grey nodes represent links to other spaceflight Risks. This DAG is a draft and has not been reviewed or approved by the Human System Risk Board.

- Altered Gravity removes (0 g) or reduces (partial g) the hydrostatic pressure gradient, causing a cephalad Fluid Shifts within the arterial and venous systems and within the cerebrospinal fluid column. Individual Factors such as age, sex, genetic predispositions, pre-existing medical conditions and more influence variability in biologic response to the spaceflight environment. This can affect multiple nodes discussed below.
- These cause physiologic changes including Venous Congestion and possibly Intracranial Pressure Changes in the brain. CO2 (Risk) and Sleep (Risk) may have a causal connection to Intracranial Pressure Changes as CO2 is known to cause vasodilation of cerebral arterioles, and impaired sleep may reduce lymphatic/glymphatic clearance from the brain and eye. Invasive measures of Intracranial Pressure Changes have not been obtained in-flight.
- These physiologic changes are hypothesized to underlie the structural changes in the eye including Optic Disc Edema, Globe Flattening, and Chorioretinal Folding. Terrestrially, Optic Disc Edema can lead to Retinal Nerve Fiber Layer Atrophy but this has not been observed in the astronaut population.
- In-mission, these structural changes lead to functional changes in the eye including Refractive Error Shifts, and reversible Visual Field Defects have been detected postflight. These in turn affect Individual Readiness for mission tasks that can progressively affect Crew Capability and Task Performance overall.
- Cardiovascular (Risk) may have a causal connection to the possibility of vascular disruption and leakage at the blood-retinal and/or blood-brain barrier resulting from radiation exposure beyond low earth orbit.
- Brain Structural Changes are hypothesized to result from the cephalad fluid shift, but potential acute effects and/or Long Term Health Outcomes are unknown.
- To characterize the risk, Surveillance is required to Detect Long Term Health Outcomes that may present as cognitive or visual decrements post-flight or post-career.
- To assess and counteract the SANS issues in flight, the Vehicle Design must include a Crew Health and Performance System that provides mass and volume allocations for several countermeasure pathways. Inclusion of these are affected by the HSIA (Risk).
- Medical Prevention Capabilities include:
    - Astronaut Selection affects and limits the Individual Factors present in the crewmembers. Those Individual Factors affect the degree of biovariability of multiple nodes including Brain Structure Changes, Intracranial Pressure Changes, Vascular Congestion, Optic Disc Edema, Globe Flattening, Chorioretinal Folds, Retinal Nerve Fiber Layer Atrophy, Refractive Error Shift and Visual Field Defects. This does not imply that all outcomes that may be influenced by Individual Factors are assessed at Astronaut Selection.
    - Lower Body Negative Pressure is under consideration as a preventive countermeasure for many effects of Fluid Shifts.
    - Veno-occlusive Thigh Cuffs may reduce Fluid Shifts and may improve Venous Congestion and Intracranial Pressure Changes.
    - Supplements such as B vitamins are hypothesized to affect homocysteine pathways and improve microvascular function and reduce edema. These are related to the Food and Nutrition (Risk).

  - Medications have been considered to prevent Intracranial Pressure Changes and these are affected by the Pharm (Risk)

- Monitoring Capabilities include:

  - Optical Coherence Tomography is used pre-, post-, and in-flight to assess the retina, choroid, and optic nerve head.
  - In-flight Fundoscopy to assess gross structural changes in the optic nerve head and retina
  - Pre- and post-flight MRI to track structural changes in the eye and brain.
  - Pre-, post-, and in-flight Ultrasound to assess structural changes within and posterior to the eye
  - Testing for Visual Acuity and Visual Fields assess the functional state of the eye. These allow us to Detect Visual Changes and guide Medical Treatment Capability in-mission.
  - In-Flight direct Intracranial Pressure Monitoring is of interest but has not been performed to date. It is speculated that this information could enable us to Detect Intracranial Pressure Changes and that information could be used to guide Medical Treatment Capabilities in the future.

- Medical Treatment Capabilities

  - Corrective Lenses are the current treatment modality in-mission for visual changes that may affect Individual Readiness. This requires the ability to provide corrective lenses with the appropriate corrective power.
  - There is currently no proven inflight pharmaceutical treatment available for SANS.

- Flight Recertification has been affected when ocular structure changes (e.g., severe SANS findings) and Intracranial Pressure Changes have been detected post flight.

SECTION IV: KNOWLEDGE BASE

Gaps in Knowledge: Link to the current gaps on NASA's Human Research Program's Human Research Roadmap (HRR)

Based on the evidence presented above, several knowledge gaps have been identified as listed below and found at, https://humanresearchroadmap.nasa.gov. Significant research has been conducted to assess these gaps and researchers are actively working to publish their findings. Ongoing research tasks are summarized on the Human Research Roadmap. Some areas of high priority research to note include assessing if and how mission duration affects SANS. Work is ongoing to determine how spaceflight induced brain changes may be associated with SANS. In addition, research is starting to investigate the long term ocular and brain structural and functional changes. Further it remains important to determine if and how spaceflight alters intracranial pressure and cerebrospinal fluid dynamics. Potential SANS countermeasures are being investigated which include lower body negative pressure, vasoconstrictive thigh cuffs, and b-vitamin supplementation.

SANS-101: Determine the relationship between fluid shifts (intravascular, interstitial, CSF) and ocular manifestations in astronauts during spaceflight.

SANS-102: Determine the relationship between the fluid-shifts induced ocular changes and fluid shifts in the CNS, including whether elevated intracranial pressure or brain edema play a role.

SANS-103: Determine whether ground-based induced fluid shifts lead to ocular manifestations.

SANS-104: Determine whether ocular manifestations can be induced by fluid shifts in rodents and whether this model can be used for more detailed mechanistic insights.

SANS-201: Determine if altered atmospheric conditions (e.g., elevated ambient CO2, mild hypoxia from exploration atmosphere) has a contributing role in the development of ocular manifestations.

SANS-202: Determine if genetic/metabolic/anatomic dispositions and biomarkers, and sex differences have a contributing role in the development of ocular manifestations.

SANS-203: Determine if radiation has a contributing role in the development of ocular manifestations.

SANS-204: Determine if sleep/glymphatics has a contributing role in the development of ocular manifestations.

SANS-301: Develop and test mechanical countermeasures in the laboratory.

SANS-302: Test mechanical countermeasures in a strict bed rest analog.

SANS-303: Test the efficacy of AG (centrifugation)-induced fluid shift versus other mechanical countermeasures.

SANS-401: Test non-mechanical countermeasures in a strict bed rest analog.

SANS-402: Test the combination of mechanical and non-mechanical countermeasures in a strict bedrest analog.

SANS-501: Test the finalized combined mechanical/non-mechanical countermeasure in the spaceflight environment (on ISS).

Significant research has been conducted to assess these gaps and researchers are actively working to publish their findings. Ongoing research is summarized. Furthermore, research is currently funded to address these gaps. Some areas of high priority ongoing research include assessing if and how mission duration affects SANS. In addition, research is starting to investigate the long term ocular and brain structural and functional changes. Further it is important to determine ICP and CSF dynamics during spaceflight.

State of Knowledge/Future work:

Despite significant advancements in our understanding of the magnitude and prevalence of ocular findings that were first described just over a decade ago, there remain numerous gaps in our knowledge about individual risk factors, underlying mechanisms, and long-term health consequences. The evidence described throughout this document points to significant variability in the development of SANS signs among long-duration crewmembers, yet we lack the ability to predict which crewmembers have the greatest likelihood of developing clinically significant SANS signs. In addition, the mechanism leading to the development of SANS findings remains unknown, adding to the challenge of determining how best to develop countermeasure protocols for use on the ISS or future exploration-class vehicles. Perhaps most important is the need to determine if a threshold exists at which point irreversible changes in visual function develop, either during or after a mission.

With the more recent observation that spaceflight induces changes to the structure of the brain, there has been some effort to determine if a relationship exists between the structural changes presenting in the eye and those presenting in the brain, but the literature remains mixed on this topic. Whether the brain structural changes lead to the development of cognitive changes is unknown at this time.

Despite these challenges, forward work includes continued use of the strict 6˚ HDTBR model to investigate many of the unknown aspects of SANS listed above, including countermeasure development. Work is underway to begin developing protocols for countermeasures that target reversal of the headward fluid shift during spaceflight, and for the use of dietary supplements. More knowledge of ICP levels during spaceflight is required before therapeutic drugs for lowering ICP can be considered.

SECTION V: CONCLUSIONS

The significant amounts of medical data collected on astronauts before, during, and after spaceflight have helped define the prevalence of changes in ocular structure and function that develop, while simultaneously investigating possible mechanisms, predictive risk profiles, and potential countermeasures for SANS. The earliest signs of ODE develop in ~70% of crewmembers flying LDSF missions (~6 months), although only ~15% develop clinically relevant Frisén grade edema. Continued use of high-resolution OCT imaging before, during, and after spaceflight provides the best insight into the development, progression, and resolution of SANS. The development of operationally feasible countermeasures is underway and will benefit from determining if targeting lowering of ICP represents a possible and applicable countermeasure. On-going work is determining the sensitivity of measures used

to assess changes in brain structure after LDSF, and whether clinically relevant outcomes emerge in the years after return from LDSF.

Although no permanent changes to vision have emerged, a need exists to monitor crewmembers for years after return from spaceflight and to determine what role mission duration has on the risk of developing permanent changes. The identification of a SANS analog increases the possibilities for testing hypotheses to identify mechanisms, identify individual contributing factors, and develop and refine countermeasure prescriptions. The expansion of this risk to include change in brain structure and to identify the possible clinical consequences of these changes remains an area of active investigation.

REFERENCES

Alperin N, Bagci AM (2018) Spaceflight-induced visual impairment and globe deformations in astronauts are linked to orbital cerebrospinal fluid volume increase. Acta Neurochir Suppl 126:215–219. https://doi.org/10.1007/978-3-319-65798-1_44

Alperin N, Bagci AM, Lam BL, Sklar E (2013) Automated quantitation of the posterior scleral flattening and optic nerve protrusion by MRI in idiopathic intracranial hypertension. Am J Neuroradiol 34:2354–2359. https://doi.org/10.3174/ajnr.A3600

Anderson AP, Babu G, Swan JG, et al (2017) Ocular changes over 60 min in supine and prone postures. J Appl Physiol 1985 123:415–423. https://doi.org/10.1152/japplphysiol.00687.2016

Appel LJ, Frohlich ED, Hall JE, et al (2011) The importance of population-wide sodium reduction as a means to prevent cardiovascular disease and stroke: a call to action from the American Heart Association. Circulation 123:1138–1143. https://doi.org/10.1161/CIR.0b013e31820d0793

Armstrong GT, Localio AR, Feygin T, et al (2007) Defining optic nerve tortuosity. AJNR Am J Neuroradiol 28:666–671

Ashari N, Hargens AR (2020) The mobile lower body negative pressure gravity suit for long-duration spaceflight. Front Physiol 11:977. https://doi.org/10.3389/fphys.2020.00977

Atchison DA, Jones CE, Schmid KL, et al (2004) Eye shape in emmetropia and myopia. Invest Ophthalmol Vis Sci 45:3380–3386. https://doi.org/10.1167/iovs.04-0292

Balasubramanian S, Tepelus T, Stenger MB, et al (2018) Thigh cuffs as a countermeasure for ocular changes in simulated weightlessness. Ophthalmology 125:459–460. https://doi.org/10.1016/j.ophtha.2017.10.023

Barger LK, Flynn-Evans EE, Kubey A, et al (2014) Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. Lancet Neurol 13:904–912. https://doi.org/10.1016/S1474-4422(14)70122-X

Barr YR (2014) Lumbar puncture during spaceflight: operational considerations, constraints, concerns, and limitations. Aviat Space Environ Med 85:1209–1213. https://doi.org/10.3357/ASEM.3674.2014

Battisti-Charbonney A, Fisher J, Duffin J (2011) The cerebrovascular response to carbon dioxide in humans. J Physiol 589:3039–3048. https://doi.org/10.1113/jphysiol.2011.206052

Bellezza AJ, Hart RT, Burgoyne CF (2000) The optic nerve head as a biomechanical structure: initial finite element modeling. Invest Ophthalmol Vis Sci 41:2991–3000

Bellone JA, Gifford PS, Nishiyama NC, et al (2016) Long-term effects of simulated microgravity and/or chronic exposure to low-dose gamma radiation on behavior and blood–brain barrier integrity. Npj Microgravity 2:16019. https://doi.org/10.1038/npjmgrav.2016.19

Berridge CW, Waterhouse BD (2003) The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev 42:33–84

Bø SH, Lundqvist C (2020) Cerebrospinal fluid opening pressure in clinical practice - a prospective study. J Neurol 267:3696–3701. https://doi.org/10.1007/s00415-020-10075-3

Botfield HF, Uldall MS, Westgate CSJ, et al (2017) A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus. Sci Transl Med 9:404. https://doi.org/10.1126/scitranslmed.aan0972

Boulton M, Flessner M, Armstrong D, et al (1999) Contribution of extracranial lymphatics and arachnoid villi to the clearance of a CSF tracer in the rat. Am J Physiol 276:R818-823. https://doi.org/10.1152/ajpregu.1999.276.3.R818

Brazis PW, Lee AG (1998) Elevated intracranial pressure and pseudotumor cerebri. Curr Opin Ophthalmol 9:27–32. https://doi.org/10.1097/00055735-199812000-00005

Brimioulle S, Moraine JJ, Norrenberg D, Kahn RJ (1997) Effects of positioning and exercise on intracranial pressure in a neurosurgical intensive care unit. Phys Ther 77:1682–1689. https://doi.org/10.1093/ptj/77.12.1682

Buckey JC, Phillips SD, Anderson AP, et al (2018) Microgravity-induced ocular changes are related to body weight. Am J Physiol Regul Integr Comp Physiol 315:R496–R499. https://doi.org/10.1152/ajpregu.00086.2018

Casley-Smith JR, Clodius L, Földi-Börcsök E, et al (1978) The effects of chronic cervical lymphostasis on regions drained by lymphatics and by prelymphatics. J Pathol 124:13–17. https://doi.org/10.1002/path.1711240104

Casley-Smith JR, Földi-Börsök E, Földi M (1976) The prelymphatic pathways of the brain as revealed by cervical lymphatic obstruction and the passage of particles. Br J Exp Pathol 57:179–188

Chapman PH, Cosman ER, Arnold MA (1990) The relationship between ventricular fluid pressure and body position in normal subjects and subjects with shunts: a telemetric study. Neurosurgery 26:181–189

Chauhan BC, O'Leary N, AlMobarak FA, et al (2013) Enhanced detection of open-angle glaucoma with an anatomically accurate optical coherence tomography-derived neuroretinal rim parameter. Ophthalmology 120:535–543. https://doi.org/10.1016/j.ophtha.2012.09.055

Compressed Gas Association (1990) Handbook of compressed gases, Third Edition, Springer

Convertino VA, Cooke WH, Lurie KG (2005) Inspiratory resistance as a potential treatment for orthostatic intolerance and hemorrhagic shock. Aviat Space Environ Med 76:319–325

Convertino VA, Ryan KL, Rickards CA, et al (2011) Optimizing the respiratory pump: harnessing inspiratory resistance to treat systemic hypotension. Respir Care 56:846–857. https://doi.org/10.4187/respcare.01018

Degnan AJ, Levy LM (2011) Pseudotumor Cerebri: Brief Review of Clinical Syndrome and Imaging Findings. AJNR Am J Neuroradiol 32:1986–1993. https://doi.org/10.3174/ajnr.A2404

Denniston AK, Keane PA (2015) Paravascular pathways in the eye: Is there an "ocular glymphatic system"? Invest Ophthalmol Vis Sci 56:3955–3956. https://doi.org/10.1167/iovs.15-17243

Diridollou S, Maillet A, Pavy-Le Traon A, et al (2001) Use of thigh pressure cuffs to modulate simulated microgravity-induced changes in the skin measured with high-resolution B-scan ultrasound. Eur J Ultrasound Off J Eur Fed Soc Ultrasound Med Biol 13:215–226. https://doi.org/10.1016/s0929-8266(01)00135-5

Downs JC, Suh JKF, Thomas KA, et al (2003) Viscoelastic characterization of peripapillary sclera: material properties by quadrant in rabbit and monkey eyes. J Biomech Eng 125:124–131. https://doi.org/10.1115/1.1536930

Draeger J, Schwartz R, Groenhoff S, Stern C (1995) Self-tonometry under microgravity conditions. Aviat Space Environ Med 66:568–570

Eklund A, Jóhannesson G, Johansson E, et al (2016) The pressure difference between eye and brain changes with posture. Ann Neurol 80:269–76. https://doi.org/10.1002/ana.24713

Fannin LA, Schiffman JC, Budenz DL (2003) Risk factors for hypotony maculopathy. Ophthalmology 110:1185–1191. https://doi.org/10.1016/S0161-6420(03)00227-6

Feola AJ, Coudrillier B, Mulvihill J, et al (2017) Deformation of the lamina cribrosa and optic nerve due to changes in cerebrospinal fluid pressure. Invest Ophthalmol Vis Sci 58:2070–2078. https://doi.org/10.1167/iovs.16-21393

Feola AJ, Myers JG, Raykin J, et al (2016) Finite element modeling of factors influencing optic nerve head deformation due to intracranial pressure. Invest Ophthalmol Vis Sci 57:1901–1911. https://doi.org/10.1167/iovs.15-17573

Feola AJ, Nelson ES, Myers J, et al (2018) The impact of choroidal swelling on optic nerve head deformation. Invest Ophthalmol Vis Sci 59:4172–4181. https://doi.org/10.1167/iovs.18-24463

Fischer WS, Wall M, McDermott MP, et al (2015) Photographic Reading Center of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT): Methods and baseline results. Invest Ophthalmol Vis Sci 56:3292–3303. https://doi.org/10.1167/iovs.15-16465

Fleischman D, Berdahl JP, Zaydlarova J, et al (2012) Cerebrospinal fluid pressure decreases with older age. PloS One 7:e52664. https://doi.org/10.1371/journal.pone.0052664

Friberg TR (1989) The etiology of choroidal folds. A biomechanical explanation. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol 227:459–464. https://doi.org/10.1007/BF02172899

Friedman DI (2007) Idiopathic intracranial hypertension. Curr Pain Headache Rep 11:62–68. https://doi.org/10.1007/s11916-007-0024-8

Friedman DI, Streeten DH (1998) Idiopathic intracranial hypertension and orthostatic edema may share a common pathogenesis. Neurology 50:1099–1104. https://doi.org/10.1212/wnl.50.4.1099

Frisén L (1982) Swelling of the optic nerve head: a staging scheme. J Neurol Neurosurg Psychiatry 45:13–18. https://doi.org/10.1136/jnnp.45.1.13

Gashev AA, Davis MJ, Delp MD, Zawieja DC (2004) Regional variations of contractile activity in isolated rat lymphatics. Microcirc N Y N 1994 11:477–492. https://doi.org/10.1080/10739680490476033

Gashev AA, Delp MD, Zawieja DC (2006) Inhibition of active lymph pump by simulated microgravity in rats. Am J Physiol - Heart Circ Physiol 290:H2295–H2308. https://doi.org/10.1152/ajpheart.00260.2005

Geddie BE, Altiparmak UE, Eggenberger ER (2010) Cup-to-disc ratio in patients with idiopathic intracranial hypertension is smaller than that in normal subjects. J Neuroophthalmol 30:231–234. https://doi.org/10.1097/WNO.0b013e3181dee8c6

Greenwald SH, Macias BR, Lee SMC, et al (2021) Intraocular pressure and choroidal thickness respond differently to lower body negative pressure during spaceflight. J Appl Physiol 1985 131:613–620. https://doi.org/10.1152/japplphysiol.01040.2020

Hamill E, Kim JD, Yalamanchili S, et al (2014) Cup-to-disc ratio in idiopathic intracranial hypertension without papilloedema. Neuroophthalmology 38:69–73. https://doi.org/10.3109/01658107.2013.874452

Hamilton DR, Sargsyan AE, Garcia K, et al (2012) Cardiac and vascular responses to thigh cuffs and respiratory maneuvers on crewmembers of the International Space Station. J Appl Physiol 1985 112:454–462. https://doi.org/10.1152/japplphysiol.00557.2011

Hansen AB, Lawley JS, Rickards CA, et al (2021) Reducing intracranial pressure by reducing central venous pressure: assessment of potential countermeasures to spaceflight-associated neuro-ocular syndrome. J Appl Physiol 1985 130:283–289. https://doi.org/10.1152/japplphysiol.00786.2020

Hansen HC, Helmke K (1996) The subarachnoid space surrounding the optic nerves. An ultrasound study of the optic nerve sheath. Surg Radiol Anat 18:323–328. https://doi.org/10.1007/BF01627611

Hargens AR, Richardson S (2009) Cardiovascular adaptations, fluid shifts, and countermeasures related to space flight. Respir Physiol Neurobiol 169 Suppl 1:S30-33. https://doi.org/10.1016/j.resp.2009.07.005

Hargens AR, Vico L (2016) Long-duration bed rest as an analog to microgravity. J Appl Physiol 1985 120:891–903. https://doi.org/10.1152/japplphysiol.00935.2015

Harris KM, Petersen LG, Weber T (2020) Reviving lower body negative pressure as a countermeasure to prevent pathological vascular and ocular changes in microgravity. NPJ Microgravity 6:38. https://doi.org/10.1038/s41526-020-00127-3

Hassler DM, Zeitlin C, Wimmer-Schweingruber RF, et al (2014) Mars' surface radiation environment measured with the Mars Science Laboratory's Curiosity rover. Science 343:1244797. https://doi.org/10.1126/science.1244797

Haykowsky MJ, Eves ND, R Warburton DE, Findlay MJ (2003) Resistance exercise, the Valsalva maneuver, and cerebrovascular transmural pressure. Med Sci Sports Exerc 35:65–68. https://doi.org/10.1249/01.MSS.0000043449.65647.C9

Hayreh SS (2016) Pathogenesis of optic disc edema in raised intracranial pressure. Prog Retin Eye Res 50:108–144. https://doi.org/10.1016/j.preteyeres.2015.10.001

Henning RA, Sauter SL, Lanphier EH, Reddan WG (1990) Behavioral effects of increased CO2 load in divers. Undersea Biomed Res 17:109–120

Herault S, Fomina G, Alferova I, et al (2000) Cardiac, arterial and venous adaptation to weightlessness during 6-month MIR spaceflights with and without thigh cuffs (bracelets). Eur J Appl Physiol 81:384–390. https://doi.org/10.1007/s004210050058

Hirvonen EA, Nuutinen LS, Kauko M (1995) Hemodynamic changes due to Trendelenburg positioning and pneumoperitoneum during laparoscopic hysterectomy. Acta Anaesthesiol Scand 39:949–955. https://doi.org/10.1111/j.1399-6576.1995.tb04203.x

Hupfeld KE, McGregor HR, Lee JK, et al (2020) The impact of 6 and 12 months in space on human brain structure and intracranial fluid shifts. Cereb Cortex Commun 1:tgaa023. https://doi.org/10.1093/texcom/tgaa023

Iliff JJ, Lee H, Yu M, et al (2013) Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. J Clin Invest 123:1299–1309. https://doi.org/10.1172/JCI67677

Iliff JJ, Wang M, Liao Y, et al (2012) A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med 4:147ra111. https://doi.org/10.1126/scitranslmed.3003748

Iwasaki K-I, Ogawa Y, Kurazumi T, et al (2021) Long-duration spaceflight alters estimated intracranial pressure and cerebral blood velocity. J Physiol 599:1067–1081. https://doi.org/10.1113/JP280318

Ji J, Shimony J, Gao F, et al (2013) Optic nerve tortuosity in children with neurofibromatosis type 1. Pediatr Radiol 43:1336–1343. https://doi.org/10.1007/s00247-013-2694-1

Johnston M (2003) The importance of lymphatics in cerebrospinal fluid transport. Lymphat Res Biol 1:41–44; discussion 45. https://doi.org/10.1089/15396850360495682

Johnston M, Zakharov A, Papaiconomou C, et al (2004) Evidence of connections between cerebrospinal fluid and nasal lymphatic vessels in humans, non-human primates and other mammalian species. Cerebrospinal Fluid Res 1:2. https://doi.org/10.1186/1743-8454-1-2

Keltner JL, Johnson CA, Cello KE, et al (2014) Baseline visual field findings in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT). Invest Ophthalmol Vis Sci 55:3200–3207. https://doi.org/10.1167/iovs.14-14243

Kiehna EN, Huffmyer JL, Thiele RH, et al (2013) Use of the intrathoracic pressure regulator to lower intracranial pressure in patients with altered intracranial elastance: a pilot study. J Neurosurg 119:756–759. https://doi.org/10.3171/2013.4.JNS122489

Koh L, Zakharov A, Johnston M (2005) Integration of the subarachnoid space and lymphatics: is it time to embrace a new concept of cerebrospinal fluid absorption? Cerebrospinal Fluid Res 2:6. https://doi.org/10.1186/1743-8454-2-6

Koppelmans V, Bloomberg JJ, Mulavara AP, Seidler RD (2016) Brain structural plasticity with spaceflight. NPJ Microgravity 2:2. https://doi.org/10.1038/s41526-016-0001-9

Kramer LA, Hasan KM, Sargsyan AE, et al (2015) Mr-derived cerebral spinal fluid hydrodynamics as a marker and a risk factor for intracranial hypertension in astronauts exposed to microgravity. J Magn Reson Imaging JMRI 42:1560–1571. https://doi.org/10.1002/jmri.24923

Kramer LA, Hasan KM, Stenger MB, et al (2020) Intracranial effects of microgravity: A prospective longitudinal MRI study. Radiology 295:640–648. https://doi.org/10.1148/radiol.2020191413

Kramer LA, Sargsyan AE, Hasan KM, et al (2012) Orbital and intracranial effects of microgravity: findings at 3-T MR imaging. Radiology 263:819–827. https://doi.org/10.1148/radiol.12111986

Kupersmith MJ, Sibony P, Mandel G, et al (2011) Optical coherence tomography of the swollen optic nerve head: deformation of the peripapillary retinal pigment epithelium layer in papilledema. Invest Ophthalmol Vis Sci 52:6558–6564. https://doi.org/10.1167/iovs.10-6782

Lagatuz M, Vyas RJ, Predovic M, et al (2021) Vascular patterning as integrative readout of complex molecular and physiological signaling by VESsel GENeration Analysis. J Vasc Res 58:207–230. https://doi.org/10.1159/000514211

Lakin WD, Stevens SA, Penar PL (2007) Modeling intracranial pressures in microgravity: the influence of the blood-brain barrier. Aviat Space Environ Med 78:932–936. https://doi.org/10.3357/asem.2060.2007

Lane HW, Bourland C, Barrett A, et al (2013) The role of nutritional research in the success of human space flight. Adv Nutr 4:521–523. https://doi.org/10.3945/an.113.004101

Laurie SS, Christian K, Kysar J, et al (2020a) Unchanged cerebrovascular CO2 reactivity and hypercapnic ventilatory response during strict head-down tilt bed rest in a mild hypercapnic environment. J Physiol 598:2491–2505. https://doi.org/10.1113/JP279383

Laurie SS, Greenwald SH, Marshall-Goebel K, et al (2021) Optic disc edema and chorioretinal folds develop during strict 6° head-down tilt bed rest with or without artificial gravity. Physiol Rep 9:e14977. https://doi.org/10.14814/phy2.14977

Laurie SS, Lee SMC, Macias BR, et al (2020b) Optic disc edema and choroidal engorgement in astronauts during spaceflight and individuals exposed to bed rest. JAMA Ophthalmol 138:165–172. https://doi.org/10.1001/jamaophthalmol.2019.5261

Laurie SS, Macias BR, Dunn JT, et al (2019) Optic disc edema after 30 days of strict head-down tilt bed rest. Ophthalmology 126:467–468. https://doi.org/10.1016/j.ophtha.2018.09.042

Laurie SS, Vizzeri G, Taibbi G, et al (2017) Effects of short-term mild hypercapnia during head-down tilt on intracranial pressure and ocular structures in healthy human subjects. Physiol Rep 5:e13302. https://doi.org/10.14814/phy2.13302

Law J, Van Baalen M, Foy M, et al (2014) Relationship between carbon dioxide levels and reported headaches on the international space station. J Occup Env Med 56:477–483. https://doi.org/10.1097/JOM.0000000000000158

Lawley JS, Babu G, Janssen SLJE, et al (2020) Daily generation of a footward fluid shift attenuates ocular changes associated with head-down tilt bed rest. J Appl Physiol 1985 129:1220–1231. https://doi.org/10.1152/japplphysiol.00250.2020

Lawley JS, Petersen LG, Howden EJ, et al (2017) Effect of gravity and microgravity on intracranial pressure. J Physiol 595:2115–2127. https://doi.org/10.1113/JP273557

Lee C, Rohr J, Sass A, et al (2020a) In vivo estimation of optic nerve sheath stiffness using noninvasive MRI measurements and finite element modeling. J Mech Behav Biomed Mater 110:103924. https://doi.org/10.1016/j.jmbbm.2020.103924

Lee H, Xie L, Yu M, et al (2015) The effect of body posture on brain glymphatic transport. J Neurosci Off J Soc Neurosci 35:11034–11044. https://doi.org/10.1523/JNEUROSCI.1625-15.2015

Lee SCM, Lueck CJ (2014) Cerebrospinal fluid pressure in adults. J Neuro-Ophthalmol Off J North Am Neuro-Ophthalmol Soc 34:278–283. https://doi.org/10.1097/WNO.0000000000000155

Lee SMC, Martin DS, Miller CA, et al (2020b) Venous and arterial responses to partial gravity. Front Physiol 11:863. https://doi.org/10.3389/fphys.2020.00863

Lee SMC, Ribeiro LC, Martin DS, et al (2020c) Arterial structure and function during and after long-duration spaceflight. J Appl Physiol 1985 129:108–123. https://doi.org/10.1152/japplphysiol.00550.2019

Lindgren KN, Kraft D, Ballard RE, et al (1998) Venoconstrictive thigh cuffs impede fluid shifts during simulated microgravity. Aviat Space Environ Med 69:1052–1058

Macias BR, Ferguson CR, Patel N, et al (2021) Changes in the optic nerve head and choroid over 1 year of spaceflight. JAMA Ophthalmol 139:663–667. https://doi.org/10.1001/jamaophthalmol.2021.0931

Macias BR, Patel NB, Gibson CR, et al (2020) Association of long-duration spaceflight with anterior and posterior ocular structure changes in astronauts and their recovery. JAMA Ophthalmol 138:553–559. https://doi.org/10.1001/jamaophthalmol.2020.0673

Mader TH, Gibson CR, Barratt MR, et al (2021) Persistent globe flattening in astronauts following long-duration spaceflight. Neuro-Ophthalmol Aeolus Press 45:29–35. https://doi.org/10.1080/01658107.2020.1791189

Mader TH, Gibson CR, Caputo M, et al (1993) Intraocular pressure and retinal vascular changes during transient exposure to microgravity. Am J Ophthalmol 115:347–350. https://doi.org/10.1016/s0002-9394(14)73586-x

Mader TH, Gibson CR, Otto CA, et al (2017) Persistent asymmetric optic disc swelling after long-duration space flight: Implications for pathogenesis. J Neuro-Ophthalmol Off J North Am Neuro-Ophthalmol Soc 37:133–139. https://doi.org/10.1097/WNO.0000000000000467

Mader TH, Gibson CR, Pass AF, et al (2011) Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight. Ophthalmology 118:2058–2069. https://doi.org/10.1016/j.ophtha.2011.06.021

Mader TH, Gibson CR, Pass AF, et al (2013) Optic disc edema in an astronaut after repeat long-duration space flight. J Neuroophthalmol 33:249–255. https://doi.org/10.1097/WNO.0b013e31829b41a6

Manzey D, Lorenz B (1998a) Joint NASA-ESA-DARA Study. Part three: effects of chronically elevated CO2 on mental performance during 26 days of confinement. Aviat Space Environ Med 69:506–514

Manzey D, Lorenz B (1998b) Mental performance during short-term and long-term spaceflight. Brain Res Brain Res Rev 28:215–221. https://doi.org/10.1016/s0165-0173(98)00041-1

Mao XW, Nishiyama NC, Byrum SD, et al (2020) Spaceflight induces oxidative damage to blood-brain barrier integrity in a mouse model. FASEB J 34:15516–15530. https://doi.org/10.1096/fj.202001754R

Marshall-Goebel K, Laurie S, Alferova I, et al (2019) Assessment of jugular venous blood flow stasis and thrombosis during spaceflight. JAMA Netw Open 2:e1915011. https://doi.org/10.1001/jamanetworkopen.2019.15011

Marshall-Goebel K, Macias BR, Kramer LA, et al (2021a) Association of structural changes in the brain and retina after long-duration spaceflight. JAMA Ophthalmol 139:781–784. https://doi.org/10.1001/jamaophthalmol.2021.1400

Marshall-Goebel K, Macias BR, Laurie SS, et al (2021b) Mechanical countermeasures to headward fluid shifts. J Appl Physiol 1985 130:1766–1777. https://doi.org/10.1152/japplphysiol.00863.2020

Marshall-Goebel K, Stevens B, Rao CV, et al (2018) Internal jugular vein volume during head-down tilt and carbon dioxide exposure in the SPACECOT study. Aerosp Med Hum Perform 89:351–356. https://doi.org/10.3357/AMHP.4934.2018

Marshall-Goebel K, Terlević R, Gerlach DA, et al (2017) Lower body negative pressure reduces optic nerve sheath diameter during head-down tilt. J Appl Physiol 1985 123:1139–1144. https://doi.org/10.1152/japplphysiol.00256.2017

Matsnev EI, Yakovleva IY, Tarasov IK, et al (1983) Space motion sickness: phenomenology, countermeasures, and mechanisms. Aviat Space Environ Med 54:312–317

Mayasnikov V, Stepanova S (2008) Features of cerebral hemodynamics in cosmonauts before and after flight on the MIR Orbital Station. In: Orbital Station MIR. Institute of BIomedical Problems: State Scientific Center of Russian Federation, pp 300–305

McComb JG, Davson H, Hyman S, Weiss MH (1982) Cerebrospinal fluid drainage as influenced by ventricular pressure in the rabbit. J Neurosurg 56:790–797. https://doi.org/10.3171/jns.1982.56.6.0790

Metzger AK, Segal N, Olson DW, et al (2018) Intrathoracic pressure regulation therapy applied to ventilated patients for treatment of compromised cerebral perfusion from brain injury. J Med Case Reports 12:178. https://doi.org/10.1186/s13256-018-1720-1

Mokri B (2001) The Monro-Kellie hypothesis: applications in CSF volume depletion. Neurology 56:1746–1748. https://doi.org/10.1212/wnl.56.12.1746

Mujat M, Lu Y, Maguluri G, et al (2019) Visualizing the vasculature of the entire human eye posterior hemisphere without a contrast agent. Biomed Opt Express 10:167–180. https://doi.org/10.1364/BOE.10.000167

Mullick AE, Zaid UB, Athanassious CN, et al (2006) Hyperhomocysteinemia increases arterial permeability and stiffness in mice. Am J Physiol Regul Integr Comp Physiol 291:R1349-1354. https://doi.org/10.1152/ajpregu.00335.2006

Murtha LA, Yang Q, Parsons MW, et al (2014) Cerebrospinal fluid is drained primarily via the spinal canal and olfactory route in young and aged spontaneously hypertensive rats. Fluids Barriers CNS 11:12. https://doi.org/10.1186/2045-8118-11-12

Nelson ES, Mulugeta L, Feola A, et al (2017) The impact of ocular hemodynamics and intracranial pressure on intraocular pressure during acute gravitational changes. J Appl Physiol 1985 123:352–363. https://doi.org/10.1152/japplphysiol.00102.2017

Nelson ES, Myers JG, Lewandowski BE, et al (2020) Acute effects of posture on intraocular pressure. PloS One 15:e0226915. https://doi.org/10.1371/journal.pone.0226915

NIOSH EID (2007) NIOSH pocket guide to chemical hazards. DHHS (NIOSH) Publication No. 2005-149

Norsk P (2020) Adaptation of the cardiovascular system to weightlessness: Surprises, paradoxes and implications for deep space missions. Acta Physiol 228:e13434. https://doi.org/10.1111/apha.13434

Osigian CJ, Grace S, Fernandez MP, et al (2018) Retinal pigment epithelium changes in pediatric patients with glaucoma drainage devices. Am J Ophthalmol Case Rep 9:23–27. https://doi.org/10.1016/j.ajoc.2017.12.001

Özel D, Erşan MC, Duran Özel B (2018) Estimating ocular hypertension and glaucoma with optic nerve tortuosity on conventional orbital magnetic resonance imaging. Can Assoc Radiol J 69:248–252. https://doi.org/10.1016/j.carj.2018.04.003

Pardon LP, Cheng H, Chettry P, Patel NB (2020) Optic nerve head morphological changes over 12 hours in seated and head-down tilt postures. Invest Ophthalmol Vis Sci 61:21. https://doi.org/10.1167/iovs.61.13.21

Pardon LP, Cheng H, Tang RA, et al (2019) Custom optical coherence tomography parameters for distinguishing papilledema from pseudopapilledema. Optom Vis Sci 96:599–608. https://doi.org/10.1097/OPX.0000000000001408

Patel N, Pass A, Mason S, et al (2018) Optical coherence tomography analysis of the optic nerve head and surrounding structures in long-duration International Space Station astronauts. JAMA Ophthalmol 136:193–200. https://doi.org/10.1001/jamaophthalmol.2017.6226

Patel NB, Sullivan-Mee M, Harwerth RS (2014) The relationship between retinal nerve fiber layer thickness and optic nerve head neuroretinal rim tissue in glaucoma. Invest Ophthalmol Vis Sci 55:6802–6816. https://doi.org/10.1167/iovs.14-14191

Pavy-Le Traon A, Heer M, Narici MV, et al (2007) From space to Earth: advances in human physiology from 20 years of bed rest studies (1986-2006). Eur J Appl Physiol 101:143–194. https://doi.org/10.1007/s00421-007-0474-z

Petersen LG, Hargens A, Bird EM, et al (2019a) Mobile Lower Body Negative Pressure Suit as an Integrative Countermeasure for Spaceflight. Aerosp Med Hum Perform 90:993–999. https://doi.org/10.3357/AMHP.5408.2019

Petersen LG, Lawley JS, Lilja-Cyron A, et al (2019b) Lower body negative pressure to safely reduce intracranial pressure. J Physiol 597:237–248. https://doi.org/10.1113/JP276557

Petersen LG, Petersen JCG, Andresen M, et al (2016) Postural influence on intracranial and cerebral perfusion pressure in ambulatory neurosurgical patients. Am J Physiol Regul Integr Comp Physiol 310:R100-104. https://doi.org/10.1152/ajpregu.00302.2015

Raykin J, Forte TE, Wang R, et al (2017) Characterization of the mechanical behavior of the optic nerve sheath and its role in spaceflight-induced ophthalmic changes. Biomech Model Mechanobiol 16:33–43. https://doi.org/10.1007/s10237-016-0800-7

Resnick SM, Goldszal AF, Davatzikos C, et al (2000) One-year age changes in MRI brain volumes in older adults. Cereb Cortex N Y N 1991 10:464–472. https://doi.org/10.1093/cercor/10.5.464

Rickards CA (2019) Vive la résistance! The role of inspiratory resistance breathing on cerebral blood flow. Respir Physiol Neurobiol 265:76–82. https://doi.org/10.1016/j.resp.2018.10.001

Roberts DR, Albrecht MH, Collins HR, et al (2017) Effects of spaceflight on astronaut brain structure as indicated on MRI. N Engl J Med 377:1746–1753. https://doi.org/10.1056/NEJMoa1705129

Roberts DR, Asemani D, Nietert PJ, et al (2019) Prolonged microgravity affects human brain structure and function. AJNR Am J Neuroradiol 40:1878–1885. https://doi.org/10.3174/ajnr.A6249

Roberts DR, Inglesby DC, Brown TR, et al (2021) Longitudinal change in ventricular volume is accelerated in astronauts undergoing long-duration spaceflight. Aging Brain 1:100017. https://doi.org/10.1016/j.nbas.2021.100017

Roberts DR, Petersen LG (2019) Studies of hydrocephalus associated with long-term spaceflight may provide new insights into cerebrospinal fluid flow dynamics here on Earth. JAMA Neurol 76:391–392. https://doi.org/10.1001/jamaneurol.2018.4891

Rohr JJ, Sater S, Sass AM, et al (2020) Quantitative magnetic resonance image assessment of the optic nerve and surrounding sheath after spaceflight. Npj Microgravity 6:30. https://doi.org/10.1038/s41526-020-00119-3

Rowell LB, Blackmon JR (1988) Venomotor responses during central and local hypoxia. Am J Physiol 255:H760-764. https://doi.org/10.1152/ajpheart.1988.255.4.H760

Sakamoto M, Nakamura K, Shibata M, et al (2010) Magnetic resonance imaging findings of Terson's syndrome suggesting a possible vitreous hemorrhage mechanism. Jpn J Ophthalmol 54:135–139. https://doi.org/10.1007/s10384-009-0783-3

Sanzari JK, Muehlmatt A, Savage A, et al (2014) Increased intracranial pressure in mini-pigs exposed to simulated solar particle event radiation. Acta Astronaut 94:807–812. https://doi.org/10.1016/j.actaastro.2013.10.006

Sater SH, Sass AM, Rohr JJ, et al (2021) Automated MRI-based quantification of posterior ocular globe flattening and recovery after long-duration spaceflight. Eye Lond Engl 35:1869–1878. https://doi.org/10.1038/s41433-021-01408-1

Scahill RI, Frost C, Jenkins R, et al (2003) A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. Arch Neurol 60:989–994. https://doi.org/10.1001/archneur.60.7.989

Scott CJ, Kardon RH, Lee AG, et al (2010) Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. Arch Ophthalmol 128:705–711. https://doi.org/10.1001/archophthalmol.2010.94

Scott JM, Tucker WJ, Martin D, et al (2019) Association of exercise and swimming goggles with modulation of cerebro-ocular hemodynamics and pressures in a model of spaceflight-associated neuro-ocular syndrome. JAMA Ophthalmol 137:652–659. https://doi.org/10.1001/jamaophthalmol.2019.0459

Scott RA, Tarver WJ, Brunstetter TJ, Urquieta E (2020) Optic nerve tortuosity on Earth and in space. Aerosp Med Hum Perform 91:91–97. https://doi.org/10.3357/AMHP.5406.2020

Sibony P, Kupersmith MJ, Honkanen R, et al (2014) Effects of lowering cerebrospinal fluid pressure on the shape of the peripapillary retina in intracranial hypertension. Invest Ophthalmol Vis Sci 55:8223–8231. https://doi.org/10.1167/iovs.14-15298

Sibony P, Kupersmith MJ, Rohlf FJ (2011) Shape analysis of the peripapillary RPE layer in papilledema and ischemic optic neuropathy. Invest Ophthalmol Vis Sci 52:7987–7995. https://doi.org/10.1167/iovs.11-7918

Sibony PA, Kupersmith MJ, Feldon SE, et al (2015) Retinal and choroidal folds in papilledema. Invest Ophthalmol Vis Sci 56:5670–5680. https://doi.org/10.1167/iovs.15-17459

Sigal IA, Flanagan JG, Ethier CR (2005) Factors influencing optic nerve head biomechanics. Invest Ophthalmol Vis Sci 46:4189–4199. https://doi.org/10.1167/iovs.05-0541

Sigal IA, Flanagan JG, Tertinegg I, Ethier CR (2004) Finite element modeling of optic nerve head biomechanics. Invest Ophthalmol Vis Sci 45:4378–4387. https://doi.org/10.1167/iovs.04-0133

Smith, SM, Zwart, SR, Heer M (2015) Risk Factor of Inadequate Nutrition. Human Health and Countermeasures, NASA Human Research Program

Son C, Zapata J, Lin C (2002) Investigation of airflow and accumulation of carbon dioxide in the service module crew quarters. Soc Auto Eng Tech Rep 2002-01–2341. https://doi.org/10.4271/2002-01-2341

Stenger MB, Laurie SS, Sadda SR, et al (2019) Focus on the optic nerve head in spaceflight-associated neuro-ocular syndrome. Ophthalmology 126:1604–1606. https://doi.org/10.1016/j.ophtha.2019.09.009

Sundblad P, Orlov O, Angerer O, et al (2014) Guidelines for standardization of bed rest studies in the spaceflight context. International Academy of Astronautics, ISBN/EAN IAA: 9782917761342

Sundblad P, Orlov O, Angerer O, et al (2016) Standardization of bed rest studies in the spaceflight context. J Appl Physiol 1985 121:348–349. https://doi.org/10.1152/japplphysiol.00089.2016

Susic D, Frohlich ED (2012) Salt consumption and cardiovascular, renal, and hypertensive diseases: clinical and mechanistic aspects. Curr Opin Lipidol 23:11–16. https://doi.org/10.1097/MOL.0b013e32834d9c52

Symons JD, Zaid UB, Athanassious CN, et al (2006) Influence of folate on arterial permeability and stiffness in the absence or presence of hyperhomocysteinemia. Arterioscler Thromb Vasc Biol 26:814–818. https://doi.org/10.1161/01.ATV.0000204408.01416.16

Taibbi G, Cromwell RL, Zanello SB, et al (2016) Ocular outcomes comparison between 14- and 70-day head-down-tilt bed rest. Invest Ophthalmol Vis Sci 57:495–501. https://doi.org/10.1167/iovs.15-18530

Taibbi G, Young M, Vyas RJ, et al (2021) Opposite response of blood vessels in the retina to 6° head-down tilt and long-duration microgravity. NPJ Microgravity 7:38. https://doi.org/10.1038/s41526-021-00165-5

Theriot CA, Chevez-Barrios P, Loughlin T, et al (2020) The impact of hindlimb suspension on the rat eye: A molecular and histological analysis of the retina. Gravitational Space Res 9:86–103. https://doi.org/10.2478/gsr-2021-0007

Theriot CA, Westby CM, Morgan JLL, et al (2016) High dietary iron increases oxidative stress and radiosensitivity in the rat retina and vasculature after exposure to fractionated gamma radiation. Npj Microgravity 2:16014. https://doi.org/10.1038/npjmgrav.2016.14

Thomas M, Vajaranant TS, Aref AA (2015) Hypotony maculopathy: Clinical presentation and therapeutic methods. Ophthalmol Ther 4:79–88. https://doi.org/10.1007/s40123-015-0037-z

Van Ombergen A, Jillings S, Jeurissen B, et al (2018) Brain tissue-volume changes in cosmonauts. N Engl J Med 379:1678–1680. https://doi.org/10.1056/NEJMc1809011

Van Ombergen A, Jillings S, Jeurissen B, et al (2019) Brain ventricular volume changes induced by long-duration spaceflight. Proc Natl Acad Sci 116:10531–10536. https://doi.org/10.1073/pnas.1820354116

Vartin C V, Nguyen AM, Balmitgere T, et al (2012) Detection of mild papilloedema using spectral domain optical coherence tomography. Br J Ophthalmol 96:375–379. https://doi.org/10.1136/bjo.2010.199562

Vyas RJ, Young M, Murray MC, et al (2020) Decreased vascular patterning in the retinas of astronaut crew members as new measure of ocular damage in spaceflight-associated neuro-ocular syndrome. Invest Ophthalmol Vis Sci 61:34. https://doi.org/10.1167/iovs.61.14.34

Wall M (2017) Update on idiopathic intracranial hypertension. Neuro Clin 35:45–57. https://doi.org/10.1016/j.ncl.2016.08.004

Wall M, Kupersmith MJ, Kieburtz KD, et al (2014) The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. JAMA Neurol 71:693–701. https://doi.org/10.1001/jamaneurol.2014.133

Wang X, Lou N, Eberhardt A, et al (2020) An ocular glymphatic clearance system removes β-amyloid from the rodent eye. Sci Transl Med 12:eaaw3210. https://doi.org/10.1126/scitranslmed.aaw3210

Wostyn P, De Deyn PP (2018) The “ocular glymphatic system”: An important missing piece in the puzzle of optic disc edema in astronauts? Invest Ophthalmol Vis Sci 59:2090–2091. https://doi.org/10.1167/iovs.17-23263

Wostyn P, De Winne F, Stern C, et al (2020) Potential involvement of the ocular glymphatic system in optic disc edema in astronauts. Aerosp Med Hum Perform 91:975–977. https://doi.org/10.3357/AMHP.5670.2020

Wostyn P, Gibson CR, Mader TH (2021) The glymphatic pathway in the optic nerve: did astronauts already reveal signs of its existence? NPJ Microgravity 7:14. https://doi.org/10.1038/s41526-021-00142-y

Xie L, Kang H, Xu Q, et al (2013) Sleep drives metabolite clearance from the adult brain. Science 342:373–377. https://doi.org/10.1126/science.1241224

Yarmanova EN, Kozlovskaya IB, Khimoroda NN, Fomina EV (2015) Evolution of Russian microgravity countermeasures. Aerosp Med Hum Perform 86:A32–A37. https://doi.org/10.3357/AMHP.EC05.2015

Yuan H, Gaber MW, Boyd K, et al (2006) Effects of fractionated radiation on the brain vasculature in a murine model: Blood–brain barrier permeability, astrocyte proliferation, and ultrastructural changes. Int J Radiat Oncol 66:860–866. https://doi.org/10.1016/j.ijrobp.2006.06.043

Yuan H, Gaber MW, McColgan T, et al (2003) Radiation-induced permeability and leukocyte adhesion in the rat blood–brain barrier: modulation with anti-ICAM-1 antibodies. Brain Res 969:59–69. https://doi.org/10.1016/S0006-8993(03)02278-9

Zanello SB, Tadigotla V, Hurley J, et al (2018) Inflammatory gene expression signatures in idiopathic intracranial hypertension: possible implications in microgravity-induced ICP elevation. NPJ Microgravity 4:1. https://doi.org/10.1038/s41526-017-0036-6

Zhang J, Stringer MD (2010) Ophthalmic and facial veins are not valveless. Clin Experiment Ophthalmol 38:502–510. https://doi.org/10.1111/j.1442-9071.2010.02325.x

Zwart SR, Gibson CR, Gregory JF, et al (2017) Astronaut ophthalmic syndrome. FASEB J Off Publ Fed Am Soc Exp Biol 31:3746–3756. https://doi.org/10.1096/fj.201700294

Zwart SR, Gibson CR, Mader TH, et al (2012) Vision changes after spaceflight are related to alterations in folate- and vitamin B-12-dependent one-carbon metabolism. J Nutr 142:427–431. https://doi.org/10.3945/jn.111.154245

Zwart SR, Gregory JF, Zeisel SH, et al (2016) Genotype, B-vitamin status, and androgens affect spaceflight-induced ophthalmic changes. FASEB J 30:141–148. https://doi.org/10.1096/fj.15-278457

Zwart SR, Laurie SS, Chen JJ, et al (2019) Association of genetics and B vitamin status with the magnitude of optic disc edema during 30-day strict head-down tilt bed rest. JAMA Ophthalmol. https://doi.org/10.1001/jamaophthalmol.2019.3124

RESOURCES

- Additional Evidence- https://humanresearchroadmap.nasa.gov/Evidence/
- Human Research Roadmap (HRR) risk page - https://humanresearchroadmap.nasa.gov/Risks/
- NASA Technical Reports Server (NTRS) - https://ntrs.nasa.gov/
- Life Science Data Archive (LSDA) - https://lsda.jsc.nasa.gov/
- GeneLab - https://genelab.nasa.gov/
- HRP Computational Model Repository (CMR) - https://hrpcmr.ndc.nasa.gov/